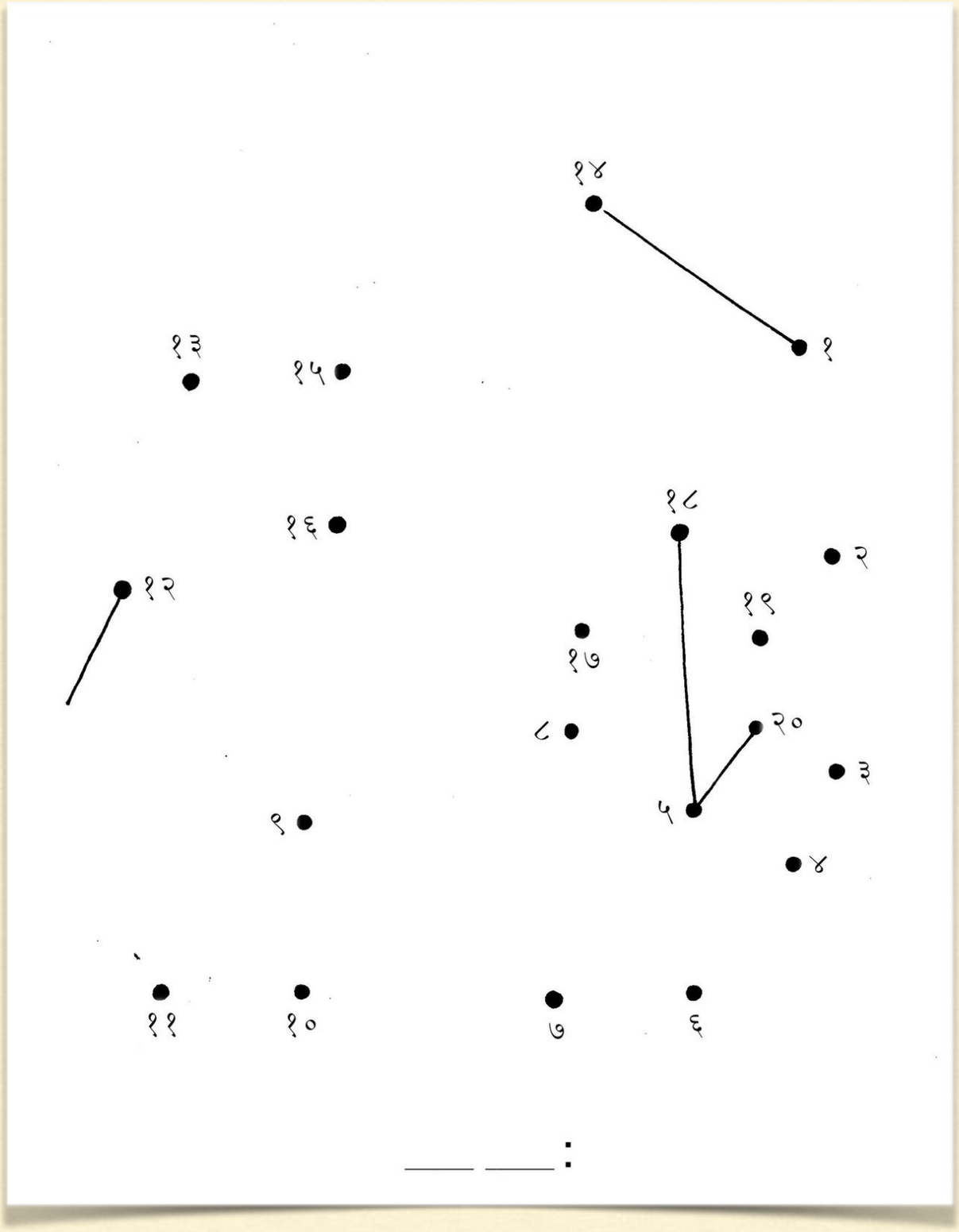
Heidi Collins, MD

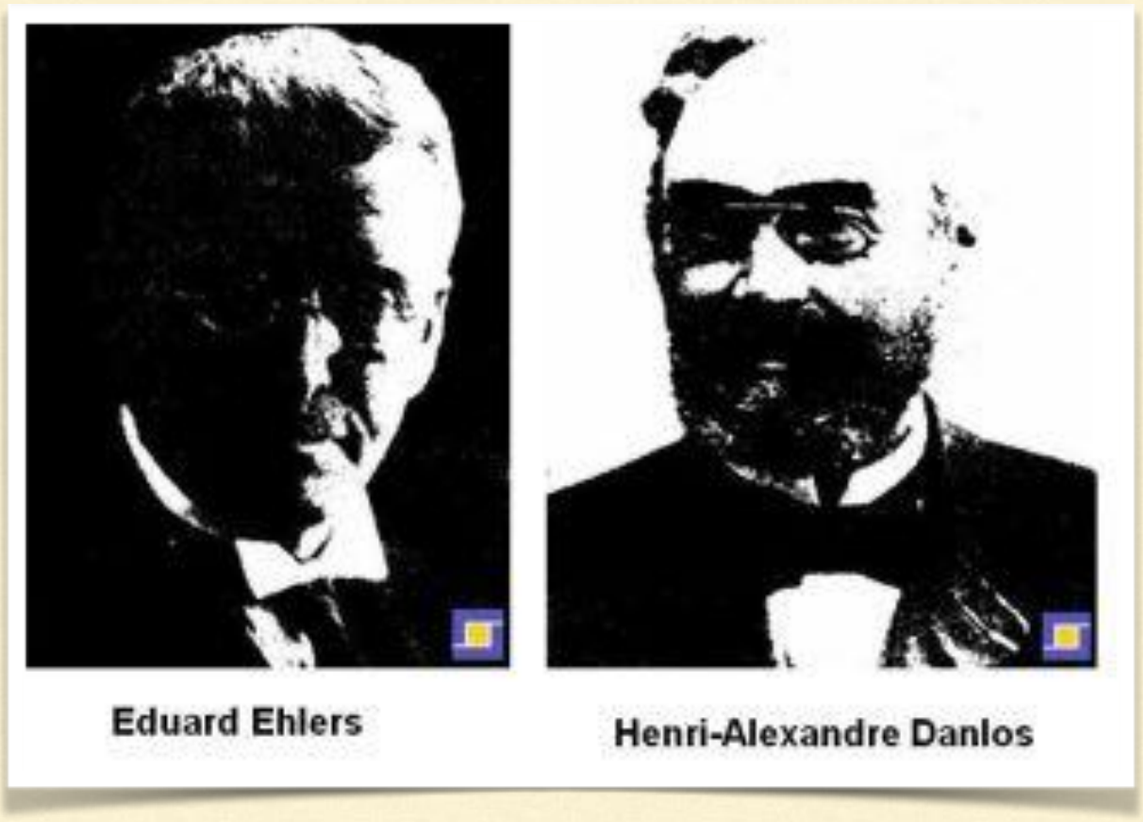
IF YOU CAN'T CONNECT THE ISSUES,

THINK CONNECTIVE TISSUES!

CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS



WHAT IS EHLERS-DANLOS SYNDROME?



- 400 B.C.: **Hippocrates**' *Airs, Waters and Places*
- 1657: Dr Job Janszoon **van Meekeren**'s case history of George Albes, a boy with hyperextensible skin
- 1892: Dr A N **Chernogubov**'s detailed association between hypermobile joints and skin findings
- 1901: Dr Edvard **Ehlers**' a case history describing a distinct disorder including lax joints, hyperextensible skin, and bruising
- 1908: Dr Henri-Alexandre **Danlos**' case history describing a disorder much like that described by Ehlers
- 1936: Frederick **Parkes-Weber** suggested "**Ehlers-Danlos Syndrome**"
- 1998: Dr Peter **Beighton *et al***'s publication of the **Villefranche** nosology classifying Ehlers-Danlos Syndromes

BUT...

WHAT *IS* EHLERS-DANLOS SYNDROME?

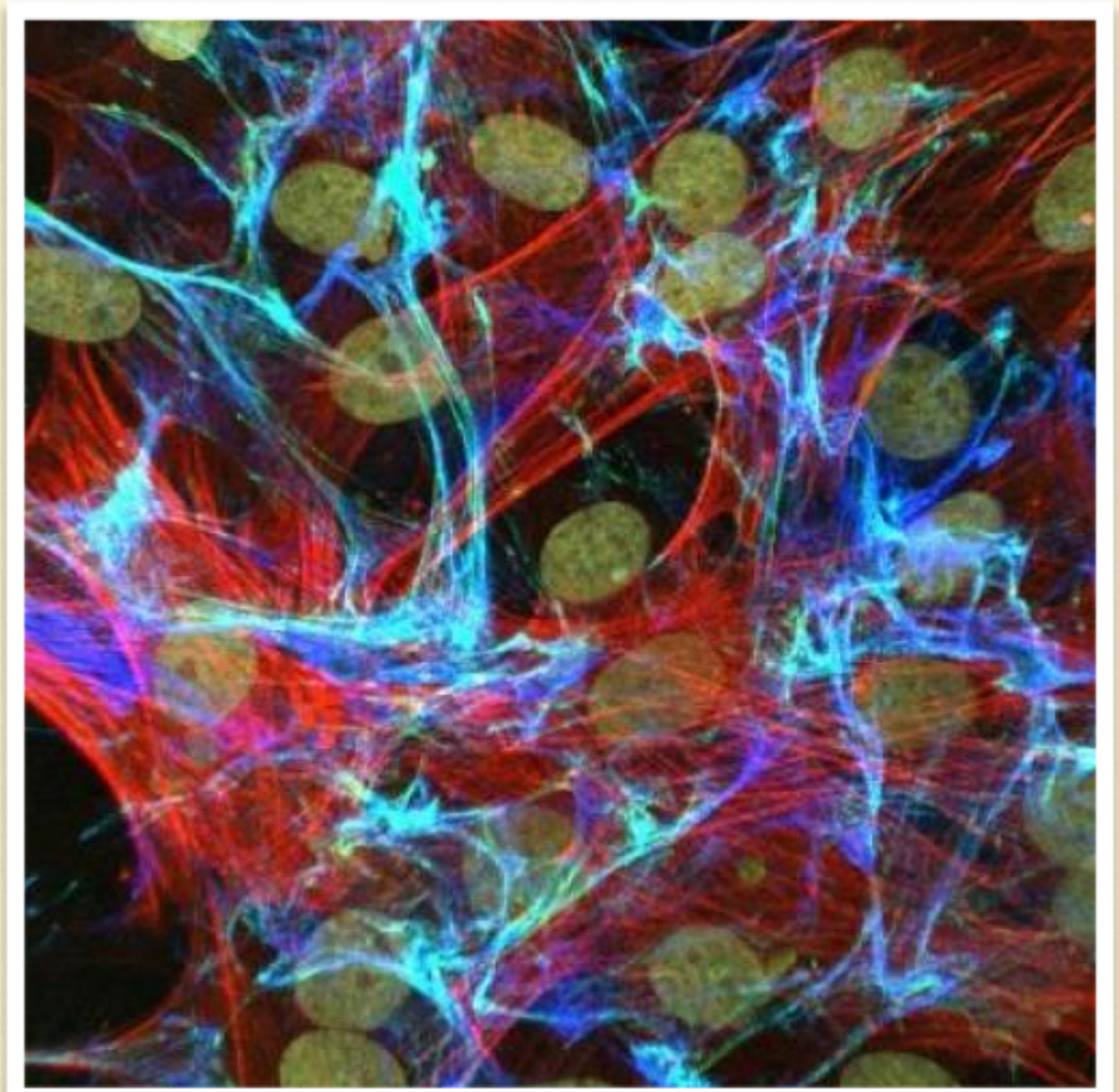
EHLERS-DANLOS SYNDROME IS A HERITABLE DISORDER OF CONNECTIVE TISSUE

- From the National Institute of Arthritis and Musculoskeletal and Rare Diseases, National Institutes of Health ***Fast Facts:*** **"What Are Heritable Disorders of Connective Tissue?"** (http://www.niams.nih.gov/Health_Info/Connective_Tissue/connective_tissue_ff.pdf)
  - Heritable Disorders of Connective Tissue (HDCTs) are **passed from parent to child**.
  - HDCTs **affect the "cellular glue"** holding tissues of the body together.
    - HDCTs **change the look, growth, or function of tissues** such as skin, bones, joints, heart, blood vessels, and numerous other organ systems.
  - **More than 200 HDCTs** are known.
    - **Ehlers-Danlos Syndrome (multiple types)**
    - Marfan Syndrome, Osteogenesis Imperfecta, Loeys-Dietz Syndrome, Stickler Syndrome, Alport Syndrome, Beal's Syndrome, Epidermolysis Bullosa, and many, many more.

WHAT *IS* CONNECTIVE TISSUE?

- Connective tissue is one of **four types of tissue** that combine to make the body.
  - **epithelial tissue**: barrier, allows selective passage (e.g. bodily surfaces, glands)
  - **muscle tissue**: contractile strength (e.g. skeletal, smooth, cardiac muscle)
  - **nervous tissue**: information highway (e.g. brain, spinal cord, peripheral nerves)
  - **connective tissue: supports, connects, and separates other tissues**
- **Organs** are made of various combinations of epithelial, muscle, nervous, and connective tissue.
- Connective tissue fills the **spaces between the organs**.

STRUCTURE OF CONNECTIVE TISSUE



- **Cells** (e.g. **fibroblasts**, adipocytes, chondroblasts, osteoblasts, erythrocytes, leukocytes, thrombocytes, mast cells, macrophages)
- **Extra-Cellular Matrix**
  - **Ground Substance**: clear, colorless gel-like fluid containing hyaluronic acid, glycosaminoglycans (e.g. chondroitin sulfate, dermatin sulfate, keratin sulfate), proteoglycans, water, and many other molecules such as fibronectin, laminin, chondronectin, and osteonectin.
  - **Fibers**: proteins
    - **collagen**: thick unbranched bundles of **collagenous fibers** promote tissue flexibility (e.g. tendons, ligaments, cartilages), while thin bundles of **reticular fibers** fill spaces (e.g. liver, spleen, lymph nodes, haematopoietic organs).
    - **elastin**: branched **elastic fibers** allow for stretch and recoil (e.g. lung, urinary bladder, skin, aorta)
  - **Microfibrils**: fiber-like strands of glycoprotein and cellulose
    - **fibrillin**: the glycoprotein essential for formation and support of elastic fibers

DIVERSITY OF CONNECTIVE TISSUE

- **Dense Connective Tissue**: fibroblasts, fibers > ground substance
  - **Regularly arranged fibers** provide **strength in one direction**, such as in tendons, ligaments, and aponeuroses
  - **Irregularly arranged fibers** distribute tissue **strength in multiple directions**, such as in fascia, joint capsules, dermis, heart valves, and digestive tract.
  - **Different fibers predominate in different tissues**. For example, **collagen** provides **tensile strength** to the dermis, tendons, ligaments, and organ sheaths, while **elastin** gives the aorta and ligamentum flavum **elasticity**.

DIVERSITY OF CONNECTIVE TISSUE (CONT'D)

- **Loose Connective Tissue**: fibroblasts, ground substance > fibers
  - **alveolar**: **wraps/cushions** organs, surrounds vessels and nerves, fills mucous membranes, plays a very important role in **inflammation and immune function** — sequestration of tissue fluids (i.e. edema), chemical signaling via mast cell degranulation, and phagocytosis of bacteria by macrophages
  - **adipose**: provides **reserve fuel** in the form of fats, **insulates** against heat loss, supports and protects organs
  - **reticular**: **lymphoid organs** such as lymph nodes, bone marrow, spleen

DIVERSITY OF CONNECTIVE TISSUE (CONT'D)

- **Cartilage**: chondrocytes, fibroblasts, chondroitin sulfate, fibers
  - **elastic**: **stretchy** (e.g. external ear, epiglottis)
  - **hyaline**: **tough**, hard (e.g. ends of long bones in joints, rib cartilage, nose, trachea, larynx)
  - **fibrocartilage**: areas of **high stress** (e.g. intervertebral discs, pubic symphysis, meniscus of knee)

DIVERSITY OF CONNECTIVE TISSUE (CONT'D)

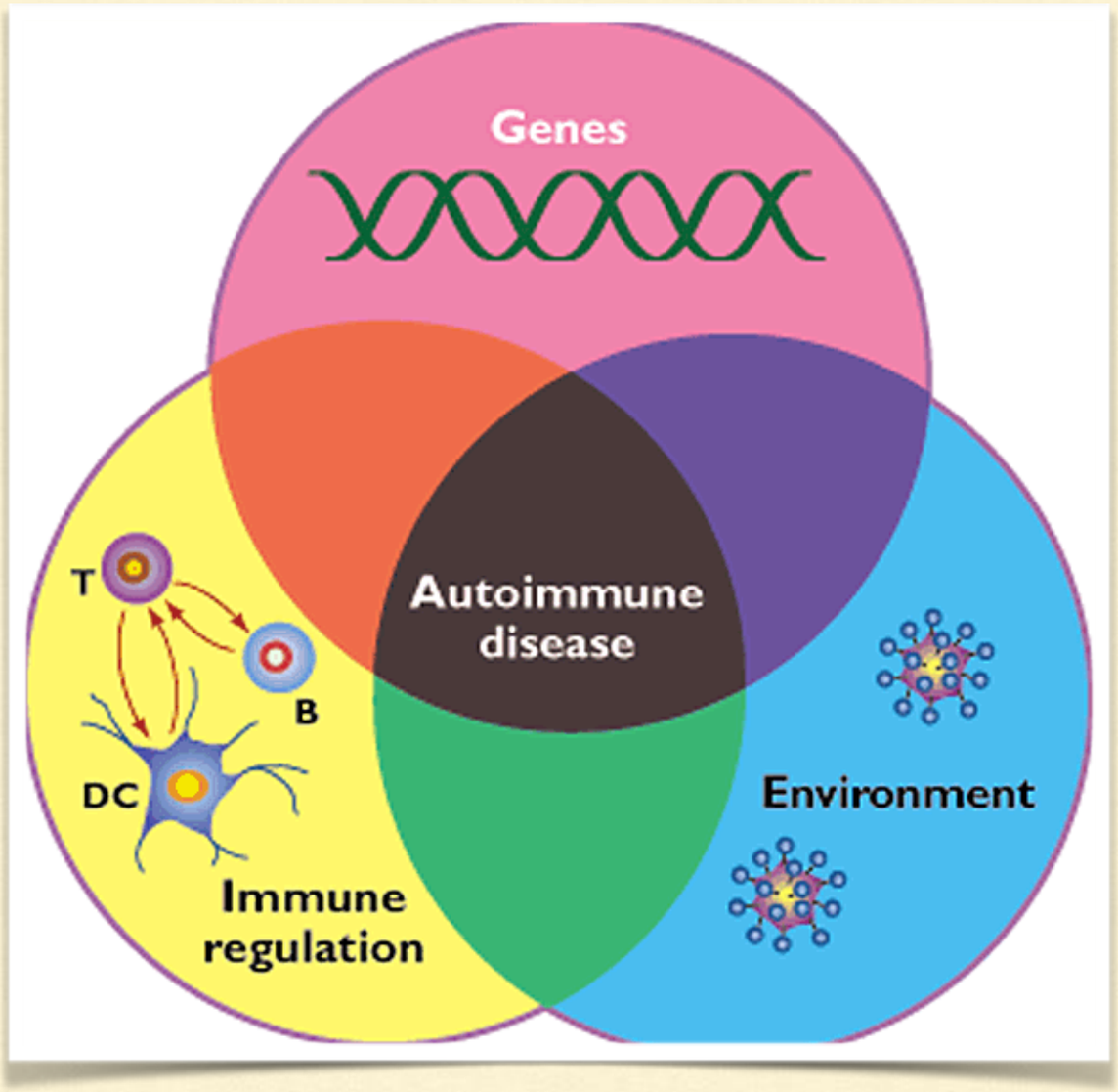
- **Specialized Connective Tissues**

  - **Bone**: osteoblasts/osteocytes in **osteoid** matrix, with **predominately Type I collagen** fibers

  - **Blood**: erythrocytes, leukocytes, and thrombocytes in a **plasma** matrix, which lacks fibrous proteins but has many **non-fibrous proteins** (e.g. immunoglobulin, fibrinogen, albumin, transferrin)

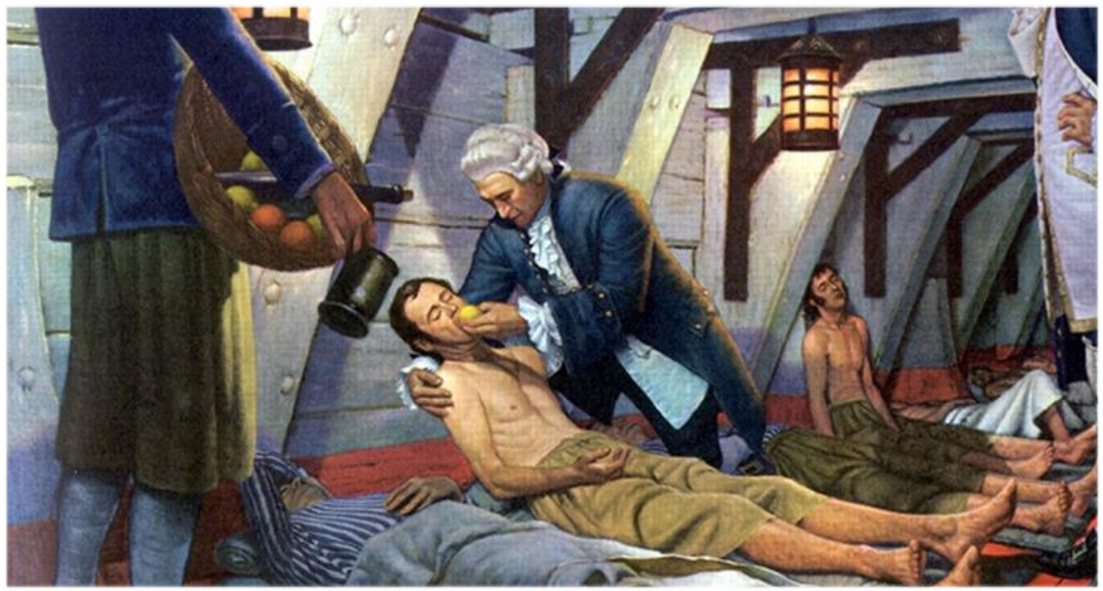
  - **Lymphatic**: leukocytes (especially lymphocytes) in **lymph** matrix, with **non-fibrous proteins**

A FEW WORDS ABOUT AUTOIMMUNE CONNECTIVE TISSUE DISORDERS



- **Autoimmune Connective Tissue Disorders** (also called **Systemic Autoimmune Diseases**, **Collagen Vascular Diseases**):
  - depend on a **triad.**
    - **genetic** factors
    - environmental **triggers**
    - **immune dysregulation**
  - include Systemic Lupus Erythematosis, Rheumatoid Arthritis, Scleroderma, Sjögren's Syndrome, Mixed Connective Tissue Disorder, Psoriatic Arthritis, Ankylosing Spondylitis, Dermatomyositis, Polyarteritis Nodosa, and many others.

A FEW WORDS ON DIETARY DEFICIENCIES AND CONNECTIVE TISSUE

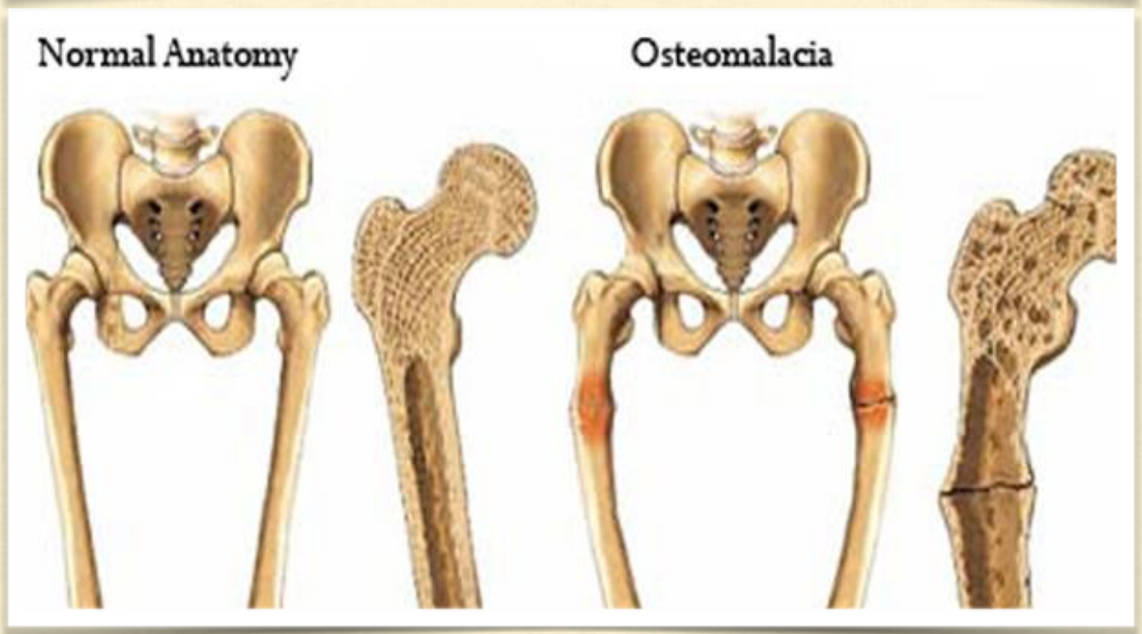


- **Vitamin C (ascorbic acid): required for collagen synthesis**; also required for conversion of folic acid to its active form and as a cofactor in synthesis of carnitine, catecholamines, peptide hormones, corticosteroids, and aldosterone
  - Citrus fruits, many other fruits, berries, vegetables, and liver offer vitamin C.
  - Preserved meats and carbohydrates contain no Vitamin C.
  - **The human body can not make its own Vitamin C.**
- **Scurvy**: The Disease of Early Explorers and Pirates
  - First became significant with the Age of Discovery
    - Vasco de Gama: 116 of 170 lost in 1499
    - Magellan: 208 of 230 lost in 1520
  - Early symptoms include malaise, lethargy, joint pain, spongy gums, discoloration of skin, **easy bruising**, **poor wound healing**.
  - Late symptoms include tooth loss, halitosis, edema, anemia, hypotension, convulsions, **extreme weakness and extreme pain**.
    - **bone pain (“ground glass osteopenia”)**
    - **muscle pain (reduced carnitine production)**
  - Death is often from fatal vessel rupture.

A FEW WORDS ON DIETARY DEFICIENCIES AND CONNECTIVE TISSUE (CONT'D)

- **Vitamin D (The Sunshine Vitamin)**: among other things, responsible for enhancing intestinal absorption of calcium, iron, magnesium, phosphate and zinc
  - **Vitamin D3 is produced in humans when ultraviolet irradiation (UV) acts on 7-dehydrocholesterol present in the skin.**
  - Fatty fish (e.g. salmon, tuna, and mackerel), fish liver oils, beef liver, cheese, and egg yolks provide **vitamin D3 (cholecalciferol)**. Some mushrooms provide vitamin **D2 (ergocalciferol)**. Fortified foods provide most of the vitamin D in the American diet.
  - **Dietary supplementation and/or sunlight exposure is necessary for certain persons to obtain sufficient vitamin D** (e.g. breastfed infants, older adults, persons with limited sun exposure, dark skin, or fat malabsorption, and persons who have undergone gastric bypass surgery).
- **Rickets (lack of adequate bone mineralization during development):** classical Vitamin D deficiency of infancy and childhood
  - Failure of bone tissue to mineralize results in skeletal deformities, soft bones with risk of fractures, dental problems, and muscle weakness/spasticity.
- **Osteomalacia (de-mineralization of bone)**: classical Vitamin D deficiency of adulthood
  - Bone demineralization weakens bones and may lead to increased risk of fractures, bone deformation, severe bone pain, and muscle weakness/spasticity.
- **Osteoporosis (loss of bone mass)**
  - Vitamin D deficiency is associated with increased parathyroid hormone (PTH) production. PTH increases bone resorption, leading to loss of bone mass.
- **Undifferentiated Connective Tissue Disorders (UCTD)**
  - Research suggests that vitamin D deficiency in UCTD patients may play a role in the subsequent progression into well-defined connective tissue disorders.

A FEW WORDS ON DIETARY DEFICIENCIES AND CONNECTIVE TISSUE (CONT'D)



- **Magnesium**: responsible for many diverse biochemical reactions in the body (e.g. ATP utilization, glycolysis, the citric acid cycle, gluconeogenesis, lipid metabolism, and protein synthesis); **mandatory for regulation of synthesis and degradation of collagen, elastin, proteoglycans, and glycoproteins.**
  - Green leafy vegetables, legumes, nuts, seeds, whole grains, avocados, potatoes, bananas, salmon, raisins, fiber-rich foods, fortified foods, and mineral waters are some sources of magnesium.
  - Only about 30-40% of dietary magnesium consumed is absorbed by the body.
  - The World Health Organization estimates that **75% of persons in the United States have dietary magnesium intake that falls below the recommended intake**.
- **Osteoporosis/Osteomalacia**
  - The mechanisms whereby **magnesium deficiency affects bone metabolism** are not clear but are probably multifactorial.
  - The formation of 1,25 dihydroxyvitamin D involves a magnesium-dependent hydroxylase enzyme. **Without adequate magnesium stores, humans are unable to fully activate vitamin D for healthy bone metabolism.**
  - The hydrogen/potassium-ATPase pump in the cells of periosteum and endosteum are magnesium dependent. The **pH of extracellular fluid in bone may fall in magnesium deficiency, resulting in demineralization**.

IMPORTANT DISTINCTIONS REGARDING EHLERS-DANLOS SYNDROME

- Ehlers-Danlos Syndrome ***IS*** a Heritable Disorder of Connective Tissue.

- Ehlers-Danlos Syndrome ***IS NOT*** an Autoimmune Connective Tissue Disorder. (Likewise, Ehlers-Danlos Syndrome ***IS NOT*** a Systemic Autoimmune Disorder ***or*** a Collagen Vascular Disorder.)

- Ehlers-Danlos Syndrome ***IS NOT*** a connective tissue disorder arising from dietary deficiencies.

BUT... REMEMBER HICKAM'S DICTUM: “PATIENTS CAN HAVE AS MANY DISEASES AS THEY DAMN WELL PLEASE.”

- **Individuals who have Ehlers-Danlos Syndrome and *also* have comorbid conditions or modifiable/unmodifiable factors directly impacting connective tissues (e.g. autoimmune disorders or certain nutritional deficiencies) are *very likely to be more severely affected overall*.**

- In order to minimize the toll taken on connective tissues, **treatable comorbidities and modifiable factors specifically affecting connective tissues *must* be recognized and maximally addressed**.

  - Allergic/autoimmune triggers must be avoided.

  - Autoimmune disorders must be addressed.

  - Healthy diet and exercise habits are essential.

  - Nutritional supplementation may be necessary to support connective tissue health (e.g. in the setting of increased nutrient requirements, malabsorption, food intolerances, or allergies).

    - enteral (i.e. orally or by feeding tube)

    - parenteral (e.g. IV, injection, topical)

NO TWO ZEBRAS HAVE THE SAME STRIPES

- **Ehlers-Danlos Syndrome occurs in tandem with comorbid conditions and modifiable or unmodifiable factors, *all combining uniquely to affect each individual as a whole.***
  - other heritable conditions (including predispositions to allergy or autoimmunity)
  - congenital conditions
  - acquired medical conditions
  - injuries (acute or chronic)
  - effects of diet (nutritional status), exercise
  - poly-pharmacy and varied pharmacogenetics
  - factors affecting access to care (e.g. geographic barriers, financial limitations, logistical issues, variable motivation and compliance)

NO TWO ZEBRAS HAVE THE SAME STRIPES

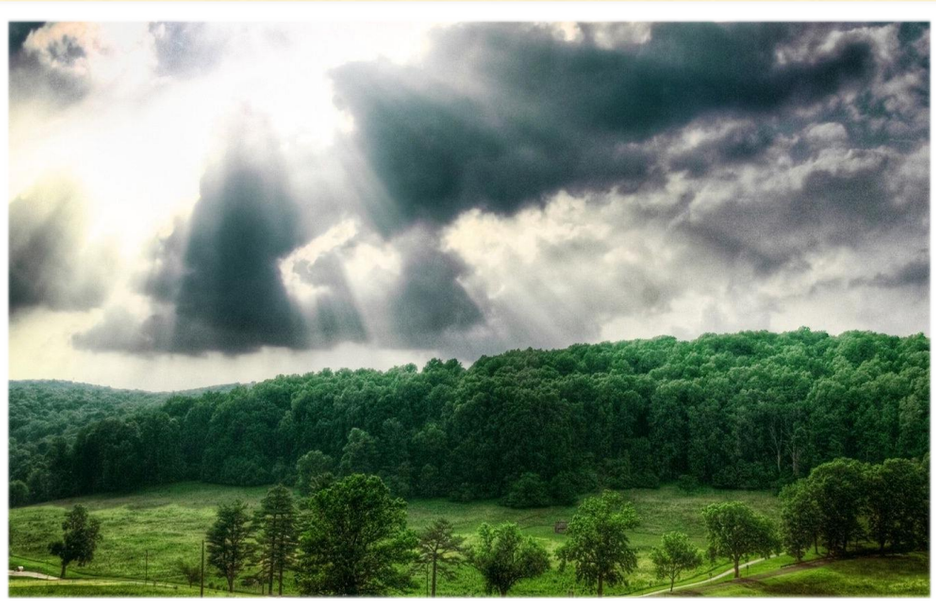
NO TWO ZEBRAS HAVE THE SAME STRIPES

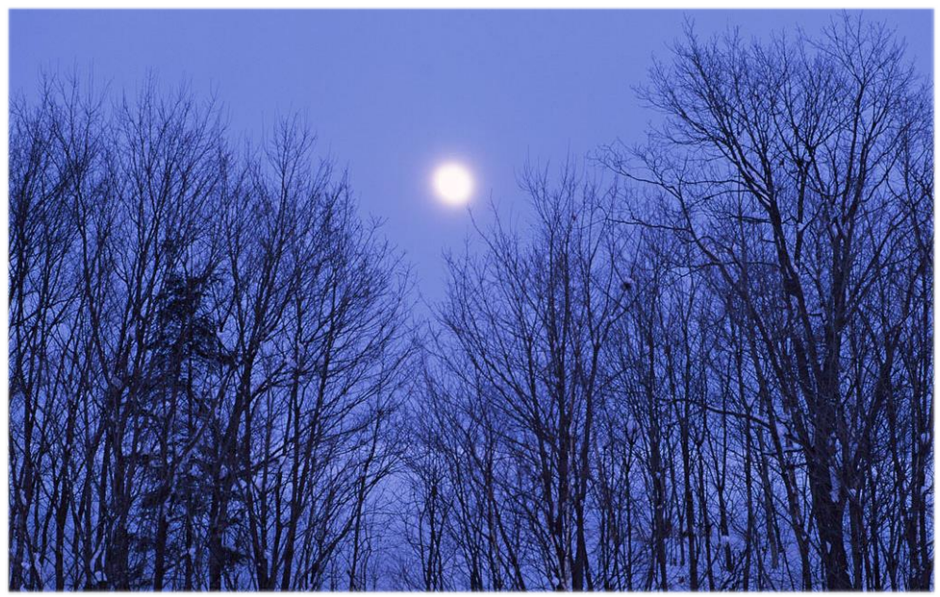
- Heterogeneity of EDS — and heterogeneity of people in general — ultimately leads to:
  - **a broad spectrum of clinical presentations**
  - **widely variable disease progressions**
  - **treatments varying in efficacy from person to person**
- "Penetrance is believed to be 100%, although **expressivity is extremely variable**, and careful examination may be required to demonstrate typical features, especially in adult men who have never experienced a major joint complication or significant pain." — Levy HP. Ehlers-Danlos syndrome, hypermobility type. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP, editors. GeneReviews. Seattle, Wash, USA: University of Washington; 2010.

EHLERS-DANLOS SYNDROME IN PRACTICE: THE FOREST AND THE TREES

- **Many clinicians lack reasonable knowledge** of EDS, its associated conditions, or patterns of clinical progression **and have little or no direct clinical experience** with EDS diagnosis or care.
- Clinicians very often **focus entirely on individual issues** ("the trees") — e.g. hypermobility, cutaneous, gastrointestinal, vascular, or autonomic concerns — **and fail to acknowledge the disorder as a whole** ("the forest").
- Clinicians who are unfamiliar with the existing body of knowledge regarding Ehlers-Danlos Syndrome **are unaware of a predictable progression of the disorder throughout the phases of life**.
  - "...**statistically significant differences by age at presentation** were registered for fatigue, myalgias, muscle cramps, strains/sprains, dislocations, tendon ruptures, tendonitis, gastroesophageal reflux, chronic gastritis, constipation/diarrhoea and abdominal hernias." — M. Castori, I. Sperduti, C. Celletti, F. Camerota, and P. Grammatico, “Symptom and joint mobility progression in the joint hypermobility syndrome (Ehlers-Danlos syndrome, hypermobility type),” Clinical and Experimental Rheumatology, vol. 29, pp. 998–1005, 2011.

EHLERS-DANLOS SYNDROME IN PRACTICE: THE FOREST AND THE TREES





EHLERS-DANLOS SYNDROME IS MORE THAN JUST HYPERMOBILITY

Joint Hypermobility Syndrome

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0889-857X/13/$ – see front matter © 2013 Elsevier Inc.

KEYWORDS

- Hypermobility • Hypermobility syndrome • Ehlers-Danlos syndrome • Dysautonomia
- Functional gastrointestinal disorder

KEY POINTS

- Joint hypermobility syndrome is a common, heritable disorder of connective tissue that is frequently overlooked.
- It is almost certainly identical to the Ehlers-Danlos Syndrome, hypermobility type.
- It is not a trivial articular problem occurring in healthy individuals; it is now recognized as a multisystemic disorder and a major source of chronic widespread pain, dysautonomias, and gastrointestinal dysmotility. It is a neglected area within rheumatology.

EHLERS-DANLOS SYNDROME IS MORE THAN JUST HYPERMOBILITY

International Scholarly Research Network
ISRN Dermatology
Volume 2012, Article ID 751768, 22 pages
doi:10.5402/2012/751768

Review Article

Ehlers-Danlos Syndrome, Hypermobility Type: An Underdiagnosed Hereditary Connective Tissue Disorder with Mucocutaneous, Articular, and Systemic Manifestations

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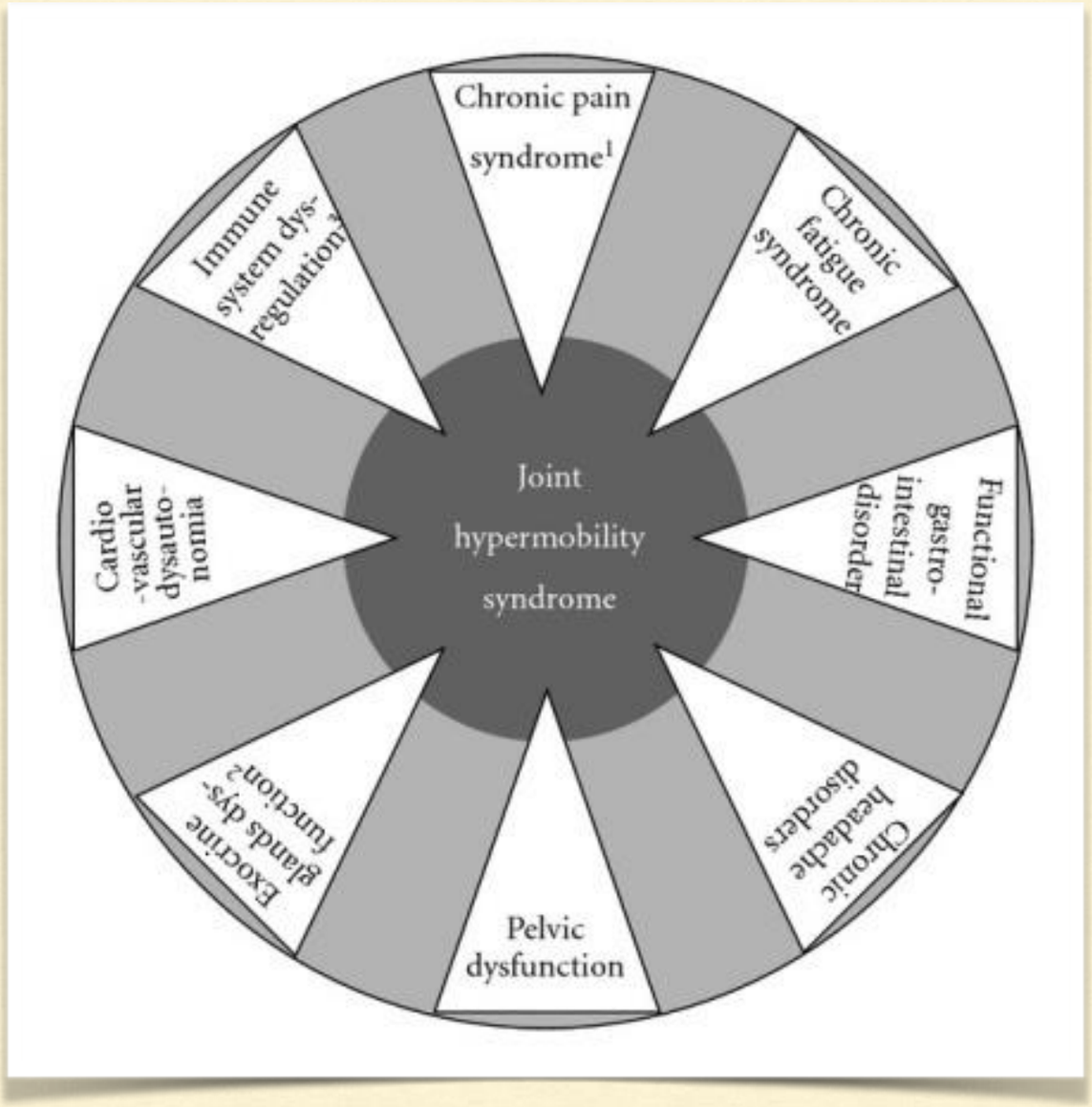
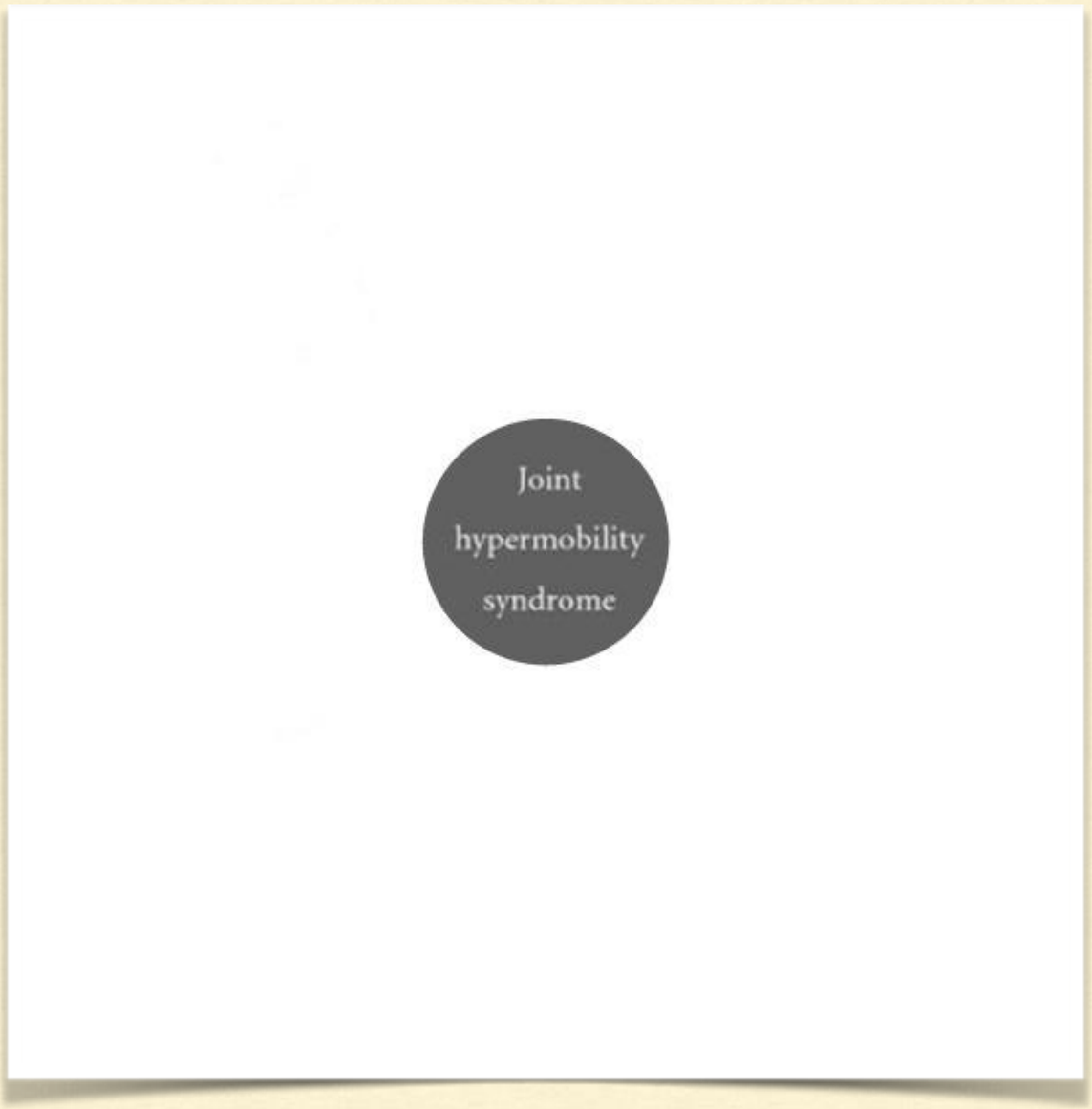
EHLERS-DANLOS SYNDROME IS MORE THAN JUST HYPERMOBILITY



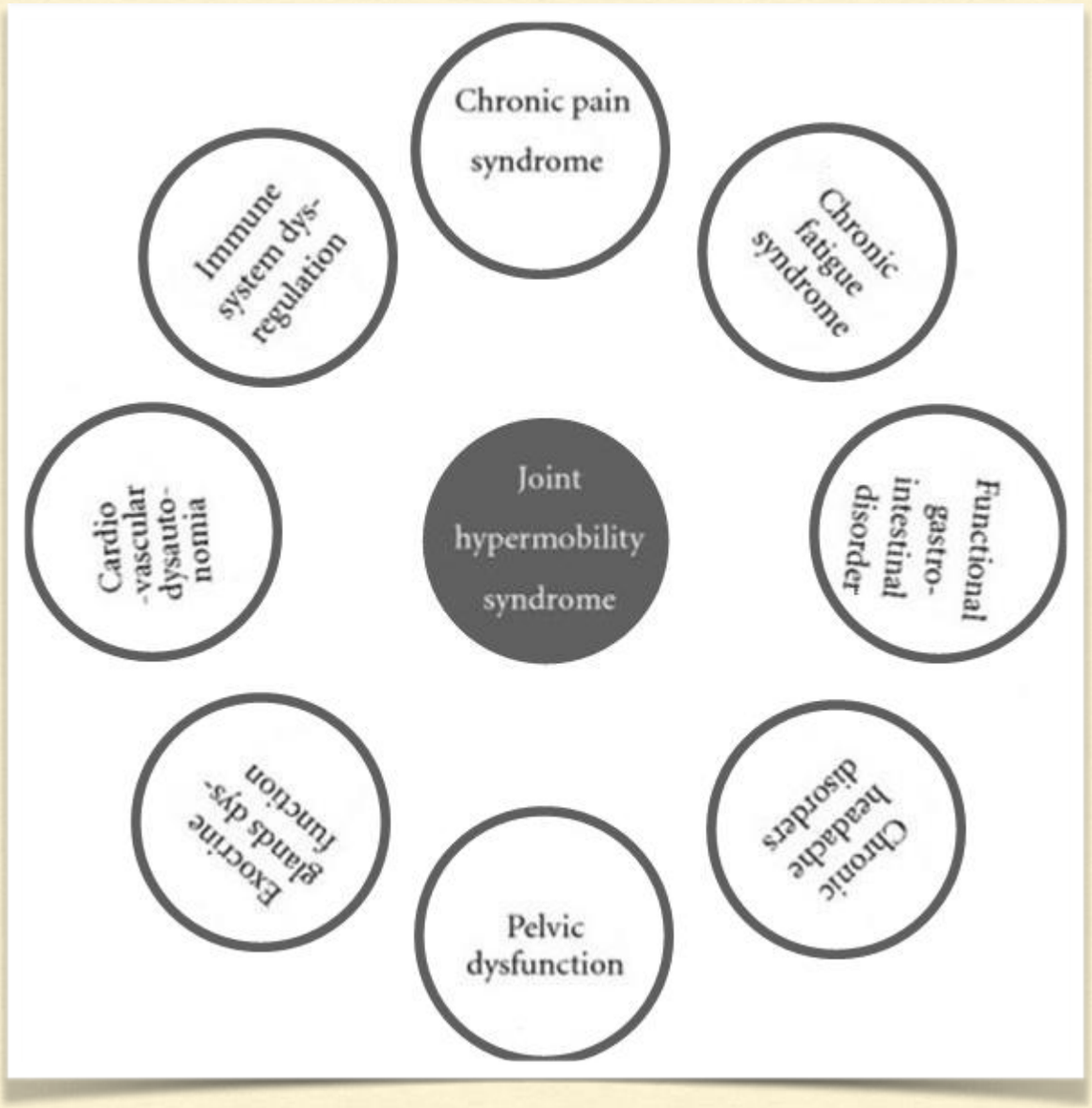
"**Schematic representation of extra-articular manifestations of Ehlers-Danlos syndrome, hypermobility type (alternatively termed joint hypermobility syndrome).** The dark grey circle symbolizes the phenotypic spectrum of this condition, which includes a series of **functional somatic syndromes** and **tissue/organ specific dysfunctions** (i.e., the white triangles, whose tips are indeed comprised within the dark circle). Outside the clinical spectrum of Ehlers-Danlos syndrome, hypermobility type, the single phenotypic components may be observed in isolation or, perhaps, in incomplete associations within the general population (the larger and light grey circle)."

EHLERS-DANLOS SYNDROME IS MORE THAN JUST HYPERMOBILITY



- Unfortunately, physicians acknowledging the possibility of EDS in a patient often do so *only* because they recognize joint hypermobility.
- Many physicians literally refuse to acknowledge EDS as a multisystem disorder.

EHLERS-DANLOS SYNDROME IS MORE THAN JUST HYPERMOBILITY



- Few clinicians have awareness or understanding of the multisystem nature of EDS.
- Clinicians may recognize **discrete issues** experienced by persons with EDS but **fail to consider them interconnected**.
- Often, multiple physicians may become involved, each seeing only the discrete issue for which they are consulted.

RECOGNIZING EHLERS-DANLOS SYNDROME: THE BLIND MEN AND THE ELEPHANT

"Thus it was that the men took turns to investigate the elephant's shape and form. As all six men were blind, neither of them could see the whole elephant and approached the elephant from different directions. After encountering the elephant, each man proclaimed in turn..."

RECOGNIZING EHLERS-DANLOS SYNDROME: THE BLIND MEN AND THE ELEPHANT

"...'O my brothers,' the first man at once cried out, 'it is as sure as I am wise that this elephant is like **a great mud wall** baked hard in the sun.'

'Now, my brothers,' the second man exclaimed with a cry of dawning recognition, 'I can tell you what shape this elephant is - he is exactly like **a spear**.' The others smiled in disbelief.

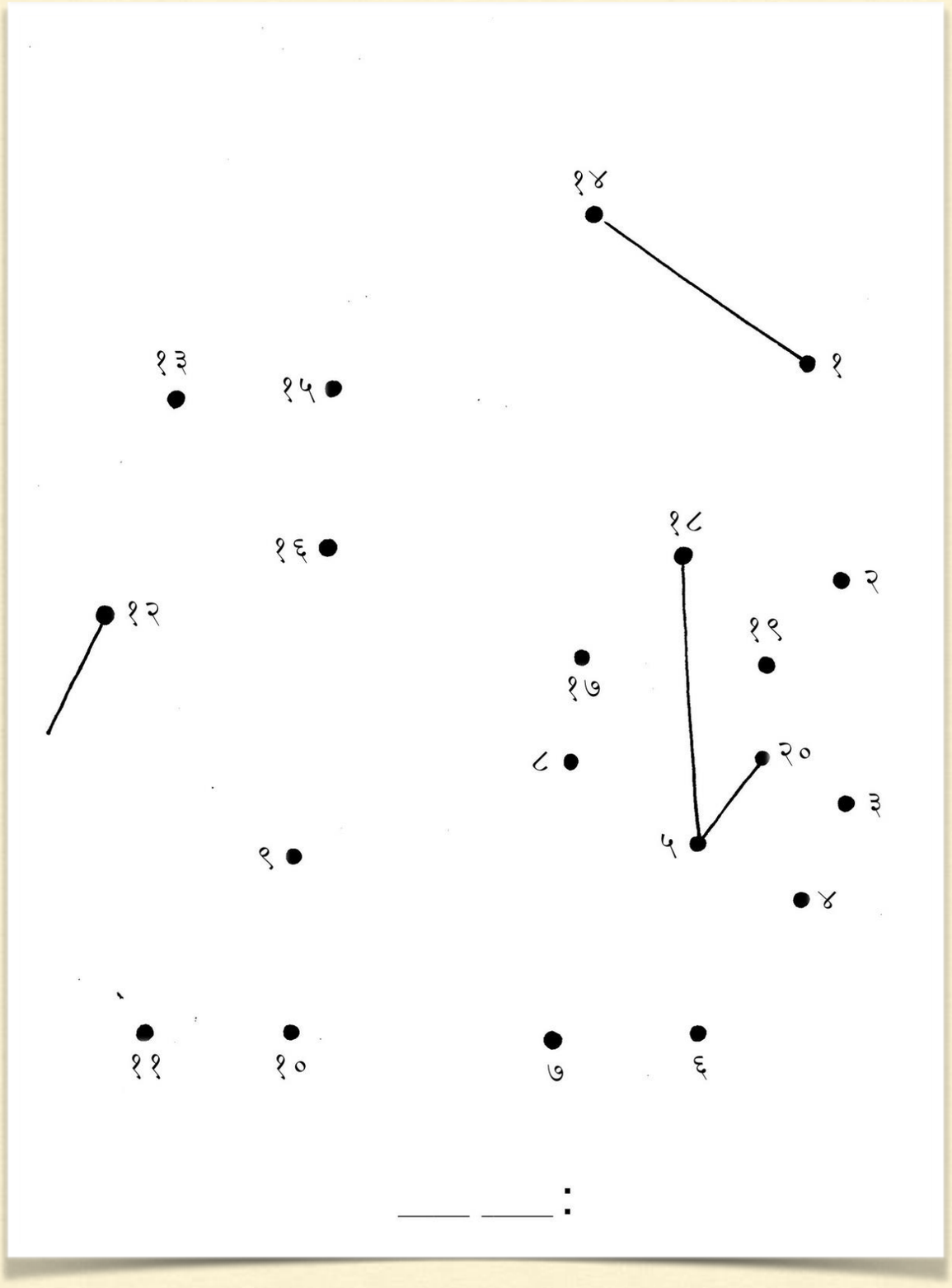
'Why, dear brothers, do you not see,' said the third man -- 'this elephant is very much like **a rope**,' he shouted.

'Ha, I thought as much,' the fourth man declared excitedly, 'This elephant much resembles **a serpent**.' The others snorted their contempt.

'Good gracious, brothers,' the fifth man called out, 'even a blind man can see what shape the elephant resembles most. Why he's mightily like **a fan**.'

At last, it was the turn of the sixth old fellow and he proclaimed, 'This sturdy pillar, brothers' mine, feels exactly like the trunk of **a great areca palm tree**.'"

HOW DO WE CONNECT THE DOTS IN EHLERS-DANLOS SYNDROME?



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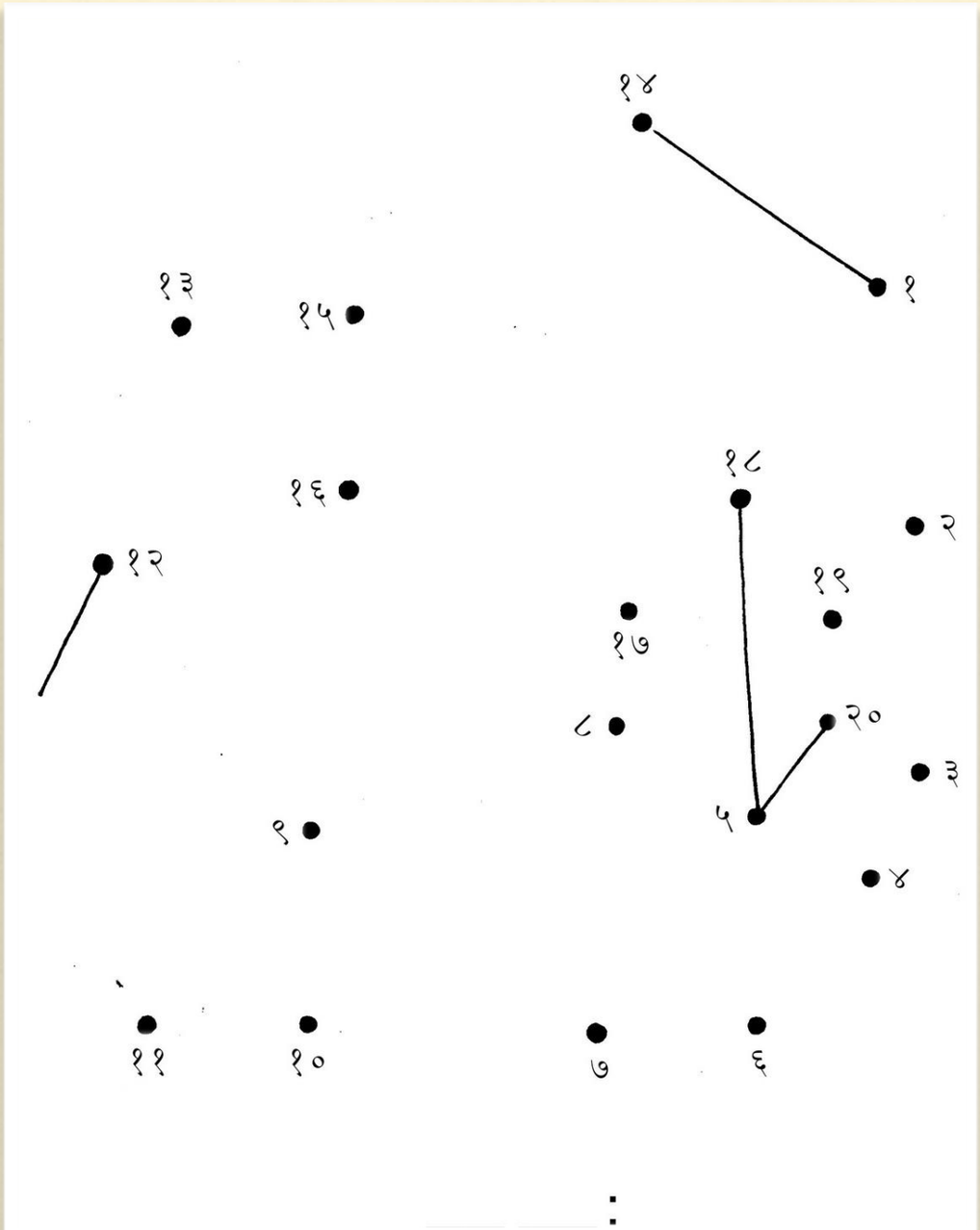
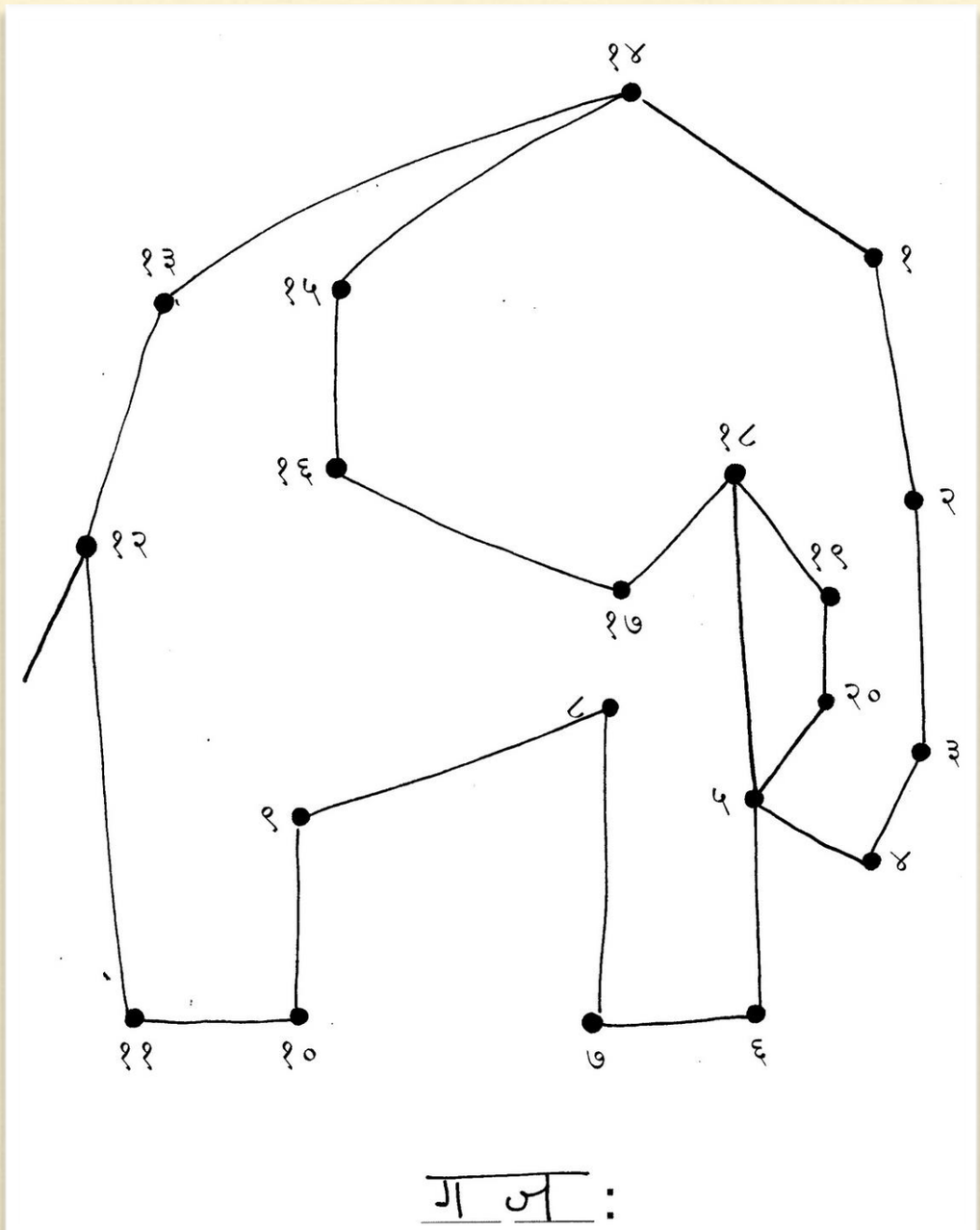




IF YOU CAN'T CONNECT THE ISSUES, THINK CONNECTIVE TISSUES.

CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS

- Ehlers-Danlos Syndrome is a group of Heritable Disorders of Connective Tissue, and **each distinct disorder is characterized by clinical symptoms and functional deficits arising from a defect in the structure, production, or processing of collagen or proteins that interact with collagen.**

- The clinical presentation of any individual EDS type derives naturally from the specific organs/tissues affected by the defect particular to that type.

- Note that **numerous EDS types are specifically *not* characterized by a mutation in a gene encoding collagen** (e.g. Hypermobility, Kyphoscoliotic, Dermatosparaxis). Instead, the defect occurs in a gene encoding a protein interacting with collagen.

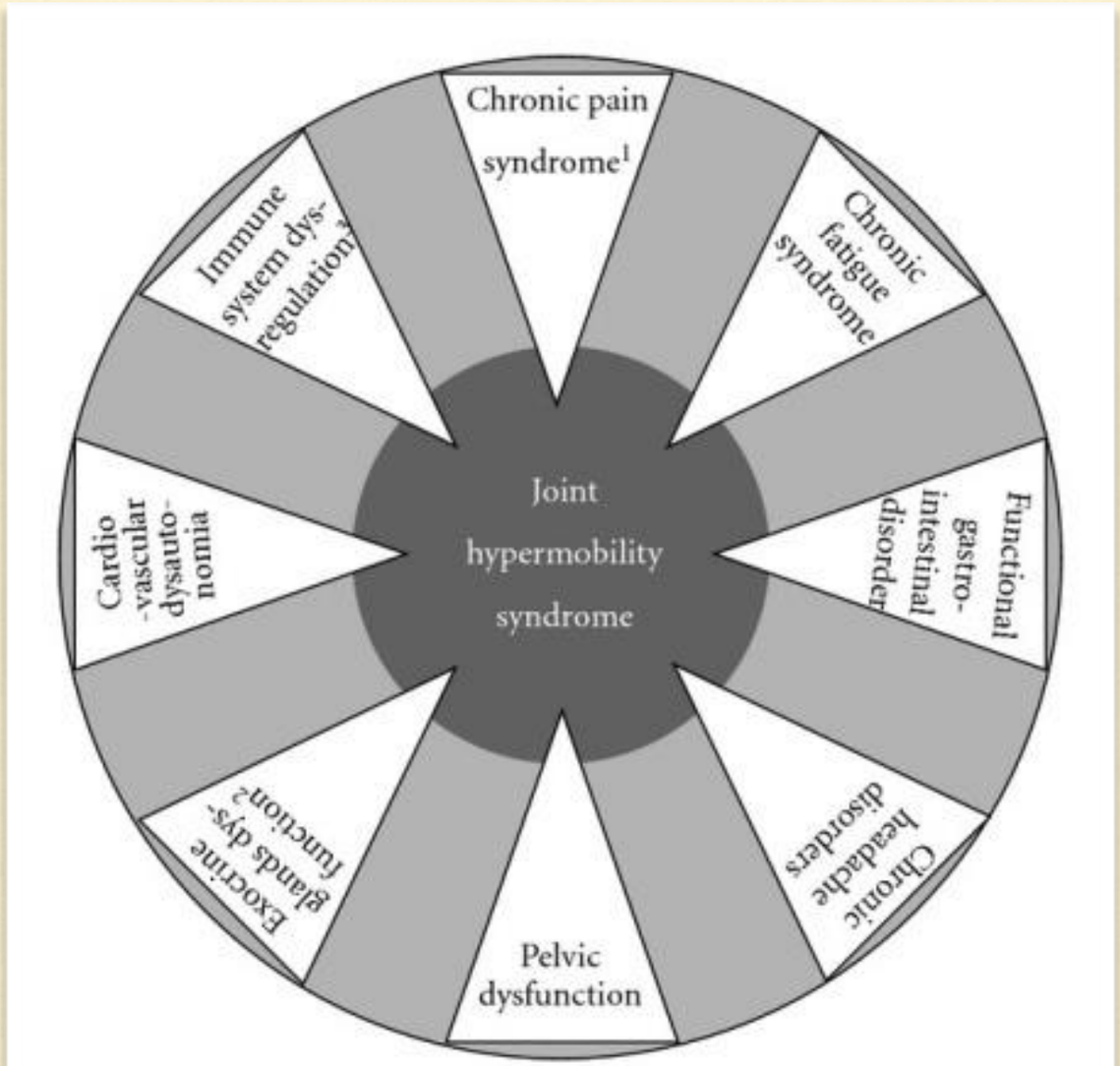
CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS

Table 1: Classification of EDSs.

Subtype	Inheritance	Gene(s)
Major forms		
Classic	AD	*COL5A1*, *COL5A2*
Hypermobility/JHS	AD?	Mostly unknown
Vascular	AD	*COL3A1*
Kyphoscoliotic	AR	*PLOD1*
Arthrochalasia	AD	*COL1A1*, *COL1A2*
Dermatosparaxis	AR	*ADAMTS2*
Rare/emerging forms		
Tenascin X deficient	AR, AD?	*TNXB*
Classic with vascular rupture	AD	*COL1A1*
Cardiac-valvular	AR	*COL1A2*
EDS/OI overlap	AD	*COL1A1*, *COL1A2*
With periventricular heterotopia	XLD	*FMNA*
Musculocontractural	AR	*CHST14*
Spondylocheirodysplastic	AR	*SLC39A13*
Progeroid	AR	*B4GALT7*
Kyphoscoliotic with deafness	AR	*FKBP14*
Parodontitis	AD	Unknown
Fibronectin deficient	AR	Unknown

AD: autosomal dominant, AR: autosomal recessive, EDS/OI: Ehlers-Danlos syndrome/osteogenesis imperfect, JHS: joint hypermobility syndrome, XLD: X-linked dominant.

HYPERMOBILITY TYPE: A PARTICULAR CHALLENGE



- The precise underlying genetic mechanism(s) at play in HEDS is (are) as yet undiscovered.
- Identifying the underlying mechanism(s) would likely:
  - allow accurate characterization of the multi-system (articular and extra-articular) **physiology** of the disorder.
  - lead to the development of objective **testing to aid in diagnosis**.
  - lead to development of **targeted treatment interventions**.
- ***Until the underlying genetic mechanism(s) at play in HEDS is (are) known, we must apply knowledge of the structure and diversity of connective tissues to best understand how the dots are connected in HEDS.***

CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS: MUSCULOSKELETAL SYSTEM

- joint laxity
  - capsuloligamentous laxity
    - hypermobility: physiologic axis(es)
    - instability: nonphysiologic axis(es)
  - subluxations/dislocations
  - sprains/strains
    - includes temporomandibular joint
- talipes equinovarus (“club foot”)
- scoliosis
- precocious arthritis
- osteopenia/osteoporosis
- muscle hypotonia/motor delay
- tendon/muscle rupture
- soft tissue lesions
  - bursitis, tendonitis, synovitis, tenosynovitis, fasciitis
- chronic limb/joint pain

Table 5: Morphologic and orthopedic features of JHS/ED-HT.

Feature
Leptosomic built or true Marfanoid habitus
Dorsal hyperkyphosis
Lumbar hyperlordosis
Scoliosis of mild degree
Fixed subluxation of the costochondral and/or sternoclavicular joints
Fixed dorsal subluxation of the distal radioulnar joint
Fixed subluxation of the first carpometacarpal joint
Cubitus valgus
Femur anteversion[1]
Patella alta or baja
Genuum valgum
Flexible flatfoot
Hallux valgus
High-arched/narrow palate
Facial asymmetry of mild degree (likely secondary to deformational plagiocephaly)

[1] Intoeing, kissing rotulae, and “W” position of the lower limbs at sitting.

CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS: MUSCULOSKELETAL SYSTEM

“While, in some patients, repeated dislocations/sprains may further weaken capsuloligamentous resistance and, thus, worsen joint instability, in others, progressive joint stiffness may progressively limit such a phenomenon.” – Castori M. Ehlers-danlos syndrome, hypermobility type: an underdiagnosed hereditary connective tissue disorder with mucocutaneous, articular, and systemic manifestations. ISRN Dermatol. 2012;2012:751768. doi: 10.5402/2012/751768. Epub 2012 Nov 22.PubMed [citation] PMID: 23227356, PMCID: PMC3512326

CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS: SKIN AND MUCOSA

- soft/velvety skin
- skin hyperextensibility (vs cutis laxa)
  - blepharoptosis (drooping eyelids)
- striae rubrae/distensae/atrophicae (“stretch marks”)
- skin fragility
- poor wound healing
  - atrophic or papyraceous (“cigarette paper”) scars
- delayed healing of bruises
- piezogenic papules
- molluscoid pseudotumors
- keratosis pilaris
- hernias (e.g. inguinal, crural, umbilical, epigastric, incisional)
- hyperhidrosis and hypohidrosis (alone or in combination)
- xerosis (e.g. xerostomia, xerophthalmia, vaginal dryness)
- mucosal fragility (e.g. epistaxis, gingival problems)
- odontogenic keratocysts
- abnormalities of lingual and inferior labial frenulum
- hypermobility (Gorlin’s Sign)

CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS: SKIN AND MUCOSA (CONT'D)

- Dental
  - dentin dysplasia
  - root dilaceration
  - hypodontia
  - ectopic eruption
  - delayed eruption
  - transmigration
  - dental fracture after minor stress
  - recurrent caries (tooth decay)
  - premature loss
  - difficulty achieving dental anesthesia
  - difficulty with hemostasis after tooth extraction
- Ocular
  - scleral discoloration (e.g. blue, grey)
  - high myopia
  - unilateral ptosis
  - vitreal abnormalities ("floaters")

CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS: GASTROINTESTINAL SYSTEM – STRUCTURAL/ANATOMIC

- Gastroesophageal Reflux Disease (GERD)
  - esophageal vs laryngotracheal reflux (“Silent Reflux”)
- organ rupture/perforation
  - ulceration
    - peptic
    - duodenal
  - diverticulae (e.g. gall bladder, small intestine, large intestine)
- hiatal hernia
- dilation
  - megaesophagus
  - megaduodenum
  - megacolon/ dolichocolon
- malrotation or volvulus
- visceroptosis
- rectocele
- rectal prolapse
- hemorrhoids

CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS: GASTROINTESTINAL SYSTEM – FUNCTIONAL/PHYSIOLOGIC

- gastrointestinal dysmotility
  - esophageal dysmotility
  - gastroparesis
  - small or large bowel dysmotility (e.g. chronic intestinal pseudoobstruction)
  - rectal evacuatory dysfunction
- Functional Gastrointestinal Disorders (Rome III Criteria)
  - Functional Esophageal Disorders (e.g. dysphagia, globus)
  - Functional Abdominal Pain Syndrome
  - Irritable Bowel Syndrome
  - Functional Diarrhea
  - Functional Constipation (e.g. chronic slow transit constipation)
  - Functional Fecal Incontinence
  - Functional Defecation Disorders
- bacterial overgrowth (dysbiosis)
- malabsorption/malnutrition with chronic nutritional deficiencies in the setting of:
  - intrinsic connective tissue abnormalities
  - inflammation (as with dysbiosis)
  - dysautonomia (e.g. too much “Fight or Flight”, not enough “Rest and Digest”)

CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS: CARDIOVASCULAR SYSTEM

- valvular abnormalities
  - regurgitation (mitral, tricuspid, aortic)
  - prolapse (e.g. Mitral Valve Prolapse)
- vascular abnormailities
  - aortic root dilatation
  - aneurysmal dilatation of aorta and other vessels
    - risk of rupture
  - vascular fragility
    - risk of hemorrhage
    - severe bruising
    - infarction of organs related to bleeding
    - capillary fragility
  - increased risk of post-operative or post-partum hemorrhage
- Dysautonomia (see Nervous System)

CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS:
NERVOUS SYSTEM: BRAIN, SPINAL CORD, PERIPHERAL NERVES

- Central Nervous System
  - headaches
  - intracranial pressure abnormalities
    - Intracranial hypertension
    - Intracranial hypotension
  - intracranial aneurysms
  - spontaneous CSF leaks
  - Chiari Malformation
  - cranio-cervical instability
  - atlanto-axial subluxation
  - cervical hyper-angulation
  - Tarlov Cysts
  - Tethered Cord Syndrome
- Peripheral Nervous System
  - neuropathy
  - pressure palsies
- Pain

CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS: NERVOUS SYSTEM: AUTONOMIC NERVOUS SYSTEM

- Dysautonomia
  - secondary
  - structural (e.g. deformation, neuropathy) vs functional
  - generalized vs focal
  - symptom predominant forms
    - Postural Orthostatic Tachycardia Syndrome: tachycardia
    - Neurocardiogenic Syncope: syncope or near-syncope
    - Neurally Mediated Hypotension: hypotension
    - Orthostatic Intolerance: intolerance of upright positions

CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS: NERVOUS SYSTEM: AUTONOMIC NERVOUS SYSTEM

- Alternative Names for POTS:
  - Hyperadrenergic orthostatic hypotension
  - Orthostatic tachycardia syndrome
  - Orthostatic intolerance
  - Postural orthostatic tachycardia syndrome
  - Hyperadrenergic postural hypotension
  - Hyperdynamic β-adrenergic state
  - Idiopathic hypovolemia
  - Orthostatic tachycardia plus
  - Sympathicotonic orthostatic hypotension
  - Mitral valve prolapse syndrome
  - Soldier’s heart
  - Vasoregulatory asthenia
  - Neurocirculatory asthenia
  - Irritable heart
  - Orthostatic anemia

CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS: IMMUNE SYSTEM

- Immune Dysregulation
  - Available medical knowledge and ample patient experience support the connection between Ehlers-Danlos Syndrome and dysregulation of gut-related immunity.
    - food allergies (often multiple)
    - other forms of inflammatory or autoimmune disorders
      - gluten intolerance
      - histamine intolerance
      - Mast Cell Activation Disorder
      - eosinophilic esophagitis
      - microcytic colitis
      - eosinophilic colitis
  - Gut-related immune dysregulation in Ehlers-Danlos Syndrome is thought to be due to a combinatoin of intrinsic connective tissue abnormalities, intestinal dysbiosis, and dysautonomia.
  - Once gut-related immunity is dysregulated, vulnerability to inflammatory and autoimmune conditions remote to the gut may be increased. This is the concept behind “Leaky Gut Syndrome”.

CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS: MISCELLANEOUS

- Pulmonary
  - asthmatic symptoms
  - impaired gas exchange
  - tracheomalacia
  - Bronchomalacia
- Gynecologic
  - irregular and/or painful menses
  - endometriosis
  - pelvic prolapse
- Possible Endocrine Abnormalities
- Multiple Obstetric Concerns
- Psychiatric
  - Multiple proposed correlations with anxiety, panic, depression, OCD, ADD/ADHD, autism/autism spectrum disorders have been proposed. More research is needed.
  - volumetrically abnormal brain regions (amygdala, anterior cingulate/parietal lobes)
  - influence of dysautonomia (e.g. excessive sympathetic nervous system activity, insomnia, or non-restorative sleep)
  - Influence of lack of proprioception

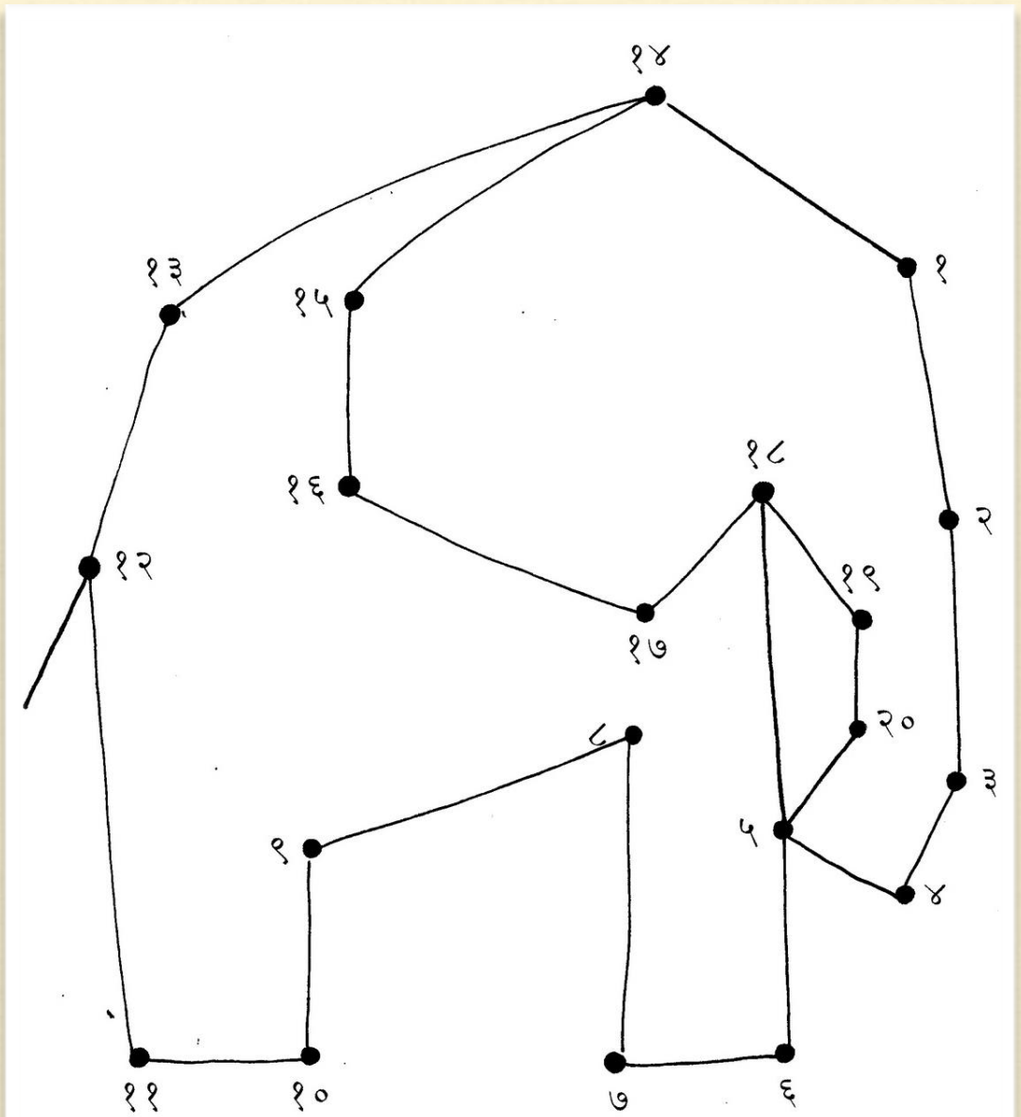
CONNECTING THE DOTS BETWEEN EHLERS-DANLOS SYNDROME AND RELATED CONDITIONS: THE BOTTOME LINE

EHLERS-DANLOS SYNDROME IS ***MORE*** THAN HYPERMOBILITY!

- Ehlers-Danlos Syndrome is a group of Heritable Disorders of Connective Tissue, and each distinct disorder is characterized by clinical symptoms and functional deficits arising from a defect in the structure, production, or processing of collagen or proteins that interact with collagen.

- The clinical presentation of any individual EDS type derives naturally from the specific organs/tissues affected by the defect particular to that type.

THE END



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