

Antrittsvorlesung

Prof. Dr. med. Markus Melloh

5. November 2015



A Twenty-Year Journey in Health Research: From the Bench to the Bedside and Beyond

Markus Melloh

Winterthur, 5 November 2015

Public Health-Relevant Factors of Back Pain

Prognostic Occupational Models for
Persistent LBP & LBP-Related Sickness Absence

Media Headlines 2013

“Antibiotics end curse of lower back pain”

The Australian

“A turning point ... we will have to re-write the textbooks”

The Telegraph

“Worthy of a Nobel prize”

The Guardian

What had happened?

2 Danish studies on LBP

- Bacterial infection & MRI changes
 - 61 patients with chronic LBP following disc herniation
 - 46% had bacterial infection, out of these 80% had Modic type 1 changes
 - conclusion: MRI changes due to edema surrounding infected disc
- AB treatment of patients with LBP and Modic type 1 changes
 - 162 patients with LBP >6 mths and Modic type 1 changes
 - RCT, 100 days AB, placebo controlled, 1-yr FU
 - conclusion: AB treatment effective in Modic-related LBP

2015

- No further headlines ... no further evidence
- 2015: Hype is over
- Just another fad?

Background

Burden of disease

- Socio-economic costs of persistent LBP significantly exceed costs of initial acute LBP episode
- Early identification of patients at risk of developing persistent LBP is essential

LBP-related sickness absence

- Prevalence of LBP-related sickness absence in 1st yr after acute LBP: 10%
- 1/5 of LBP patients have long-term sickness absence within 2 yrs

Melloh et al. *Int Orthop* 2009; Melloh et al. *Behav Med* 2013; Melloh et al. *J Back Musculoskeletal Rehabil* 2014; Melloh et al. *Australas Med J* 2015

Objectives

- Which occupational factors are identifiers for the transition from acute to persistent LBP?
- Identify baseline-predictors for LBP-related sickness absence
- Identify prognostic models for persistent LBP and LBP-related sickness absence

Study Design

Observational cohort study

Structured telephone interview; postal survey

- Baseline assessment
- Follow-up at 3, 6, 12 wks and 6 mths

Participants recruited from GP clinics

Study Flow

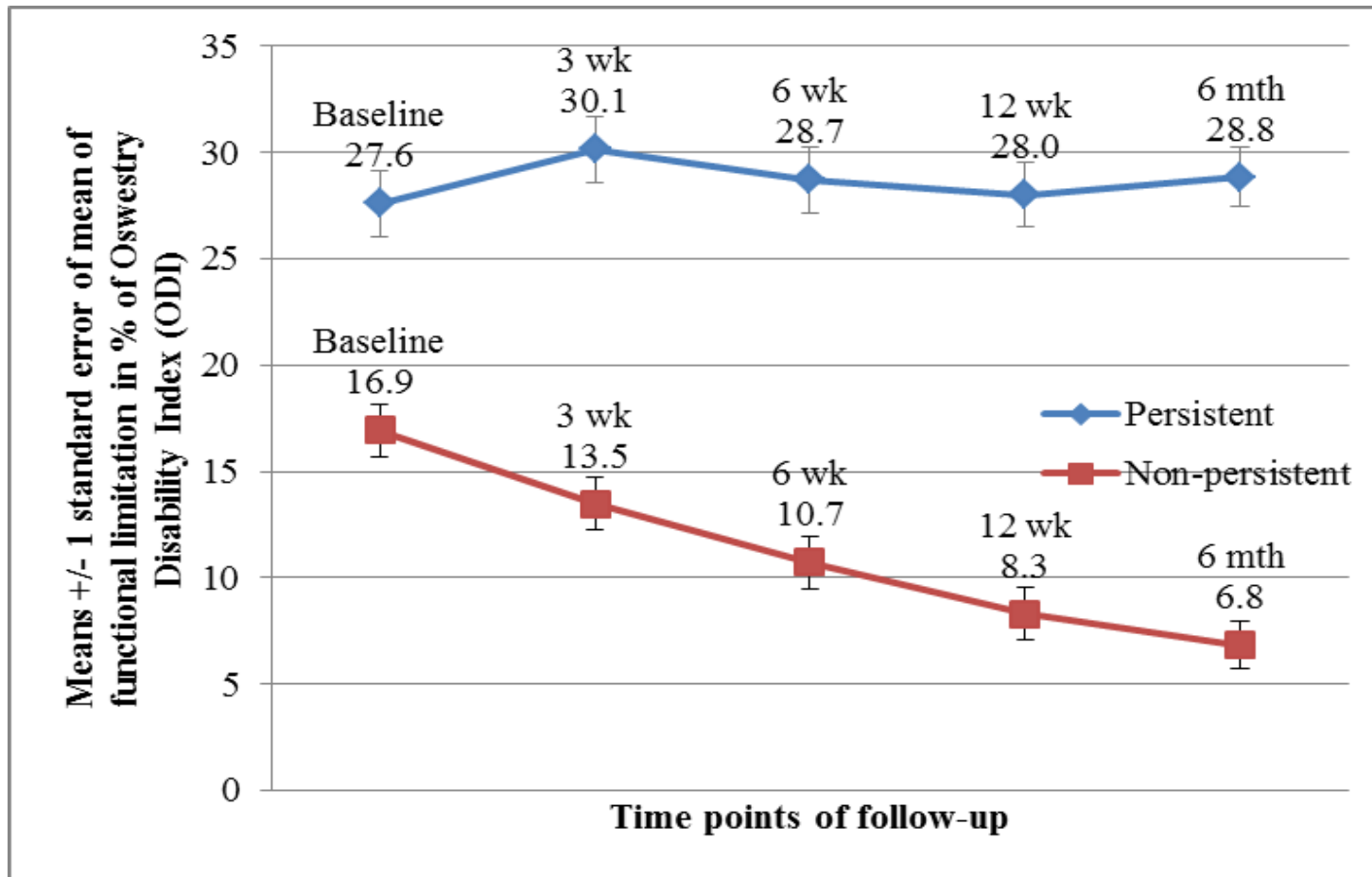
Screened: 562 participants; eligible: 438

Enrolled: 315

Completed: 169

Melloh et al. *Occup Med (Lond)* 2011; Melloh et al. *Work* 2013; Melloh et al. *Int J Occup Saf Ergonom* 2013; Melloh et al. *J Back Musculoskeletal Rehabil* 2015

Persistent vs. Non-Persistent LBP



Predictor Model for Persistent LBP

Predictors at baseline	<i>p</i>	OR	CI (OR)
Resigned attitude towards the job	0.007	1.73	1.16 - 2.59
Social support at work	0.019	0.54	0.32 - 0.90
Functional limitation	0.028	1.05	1.01 - 1.10
Duration of low back pain	0.000	1.04	1.02 - 1.06

Predictor Model for Sickness Absence

Baseline-predictor model	<i>p</i>	OR	CI (OR)
Job control	0.019	0.47	0.26 - 0.88
Resigned attitude towards the job	0.419	1.22	0.76 - 1.97
Fear-avoidance beliefs about work	0.198	1.04	0.98 - 1.11
Social support at work	0.617	1.17	0.63 - 2.20
Depression	0.030	1.09	1.01 - 1.17
Functional limitation	0.033	1.07	1.01 - 1.14
Physical health	0.328	1.05	0.96 - 1.14

Implications for Practice

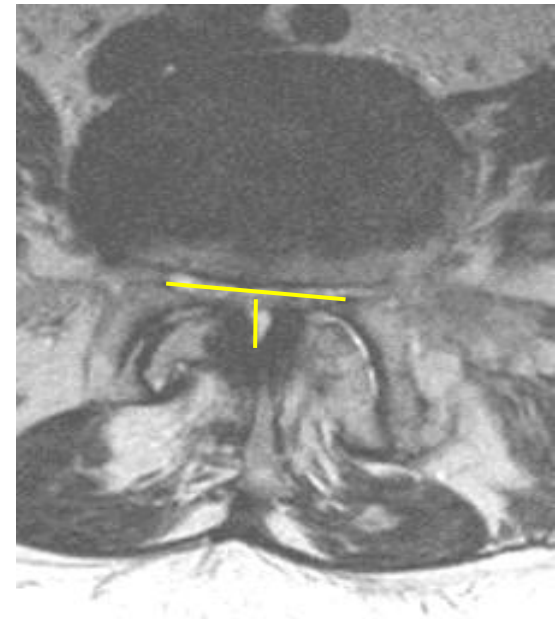
- Patients at risk should be screened for modifiable occupational risk and protective factors
- *Resigned attitude towards the job* should be considered for workplace interventions
- Higher participation in job design could prevent *resigned attitude towards the job* and persistent LBP
- *Early identification* of patients at risk of LBP-related sickness absence allows *early intervention*

New Diagnostic Tools in Spine

What is the Clinical Value of two new Decision-Making Tools in Lumbar Spinal Stenosis?

Lumbar Spinal Stenosis

- One of the most commonly diagnosed spinal disorders in patients
- Disabling and chronic condition affecting middle-aged and elderly patients
- Increasing prevalence with ageing population
- Surgery for LSS:
Most frequent spinal procedure in patients >65 yrs



Public Health Issues

- Functional limitation by pain
- Inactivity
- Patients at risk for effects of sedentary behaviour
- Societal and financial burden



Rampersaud et al. *Spine J* 2014; Melloh et al. *J Orthop Sports Phys Ther* 2011;
Melloh and Barz *Med Hypotheses* 2014

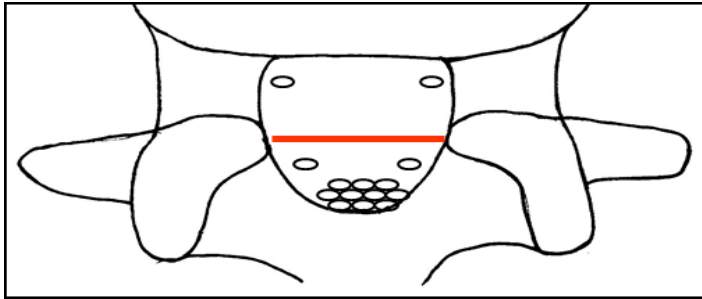
Diagnosis - Imaging

CT, MRI

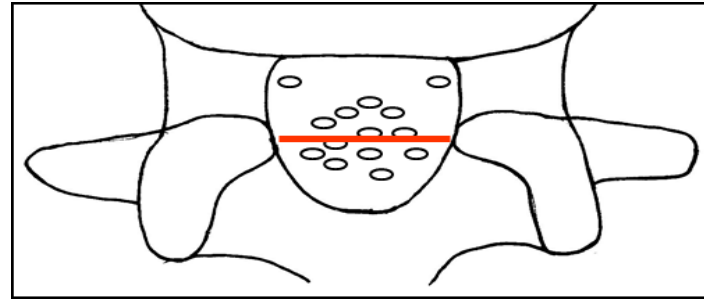
- Underdiagnosis: rapidly progressive stenosis
- Overdiagnosis: elderly patients with slow progression or adjustment reaction
- MRI findings of LSS not always correlate with clinical symptoms:
Additional tests needed
- “Simply ordering an MRI is no more useful than ordering a pizza”



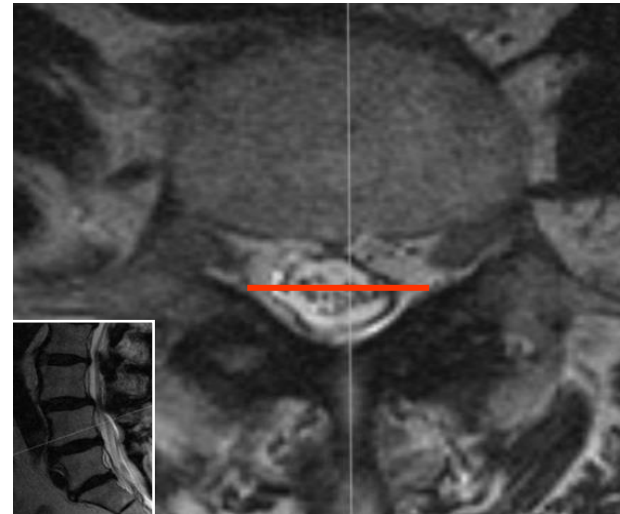
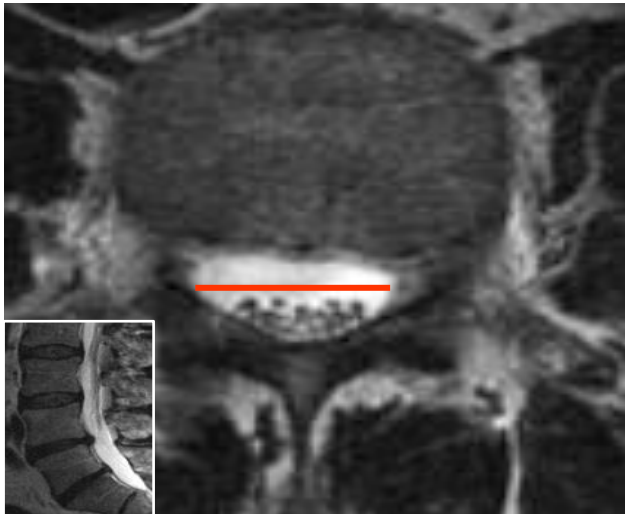
Nerve Root Sedimentation Sign



Negative Sedimentation Sign:
Normal nerve root sedimentation



Positive Sedimentation Sign:
Absent nerve root sedimentation



Study Design

- **Hypothesis:** SedSign distinguishes between patients with LSS and non-specific LBP
- Prospective case-control study
- 350 patients assessed for eligibility
- Two groups with 100 patients each:
LSS group and LBP group

Results

	<i>LSS</i>	<i>LBP</i>	<i>Total</i>
Positive SedSign	94	0	94
Negative SedSign	6	100	106
Total	100	100	200

- ⇒ 94% sensitivity
- ⇒ 100% specificity
- ⇒ Ideal sensitivity/ specificity:
measured under perfect conditions,
in highly specific patient groups

Conclusions

- SedSign distinguishes between patients with LSS and LBP
- Positive SedSign may increase sensitivity of detecting LSS
- Negative SedSign may increase specificity for ruling out LSS
- **Prospective studies needed to validate results in clinical setting**

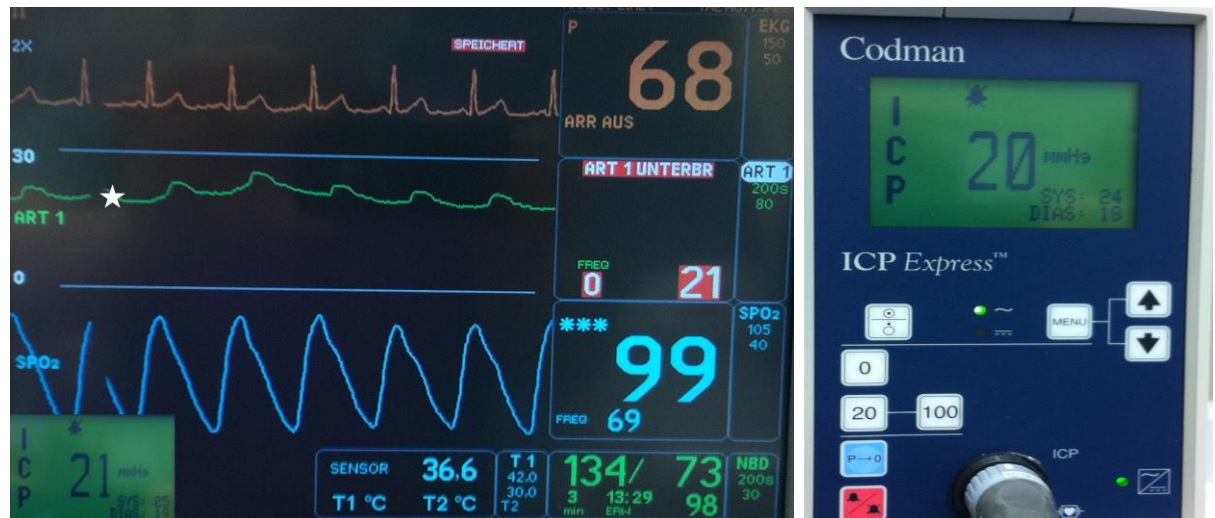
Epidural Pressure Study

- **Hypothesis:** Pos. SedSign in patients with LSS associated with increased epidural pressure at level of stenosis
- Patients without LSS / neg. SedSign
- Patients with LSS / pos. SedSign
- Codman™ catheter
(pressure sensor; single point pressure measure)



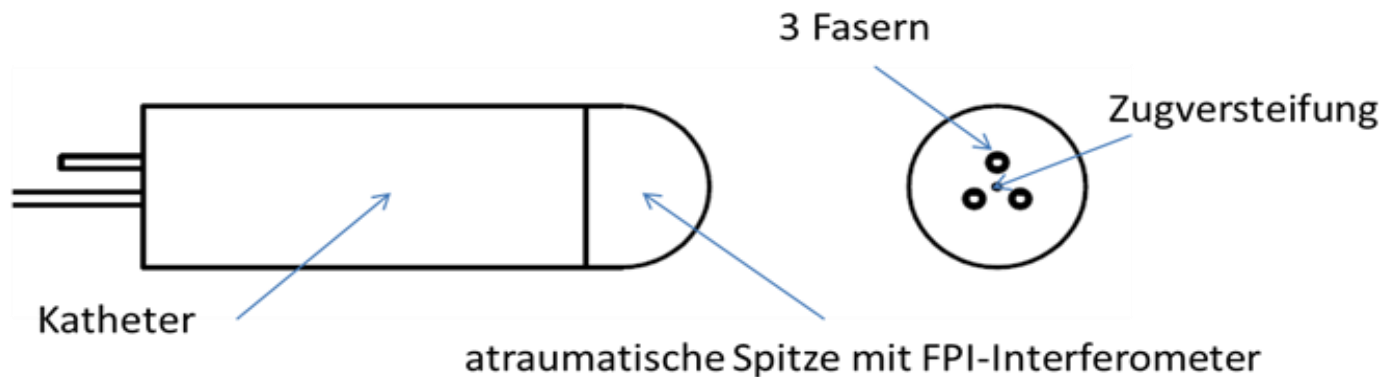
Results

- Without LSS / neg. SedSign epidural pressure 9 mmHg
- Breath and pulse-synchronous waves 1-3 mmHg
- With LSS / pos. SedSign similar pressure 8 mmHg
- At stenosis level epidural pressure 23 mmHg
- Below the stenosis no breath and pulse-synchronous wave



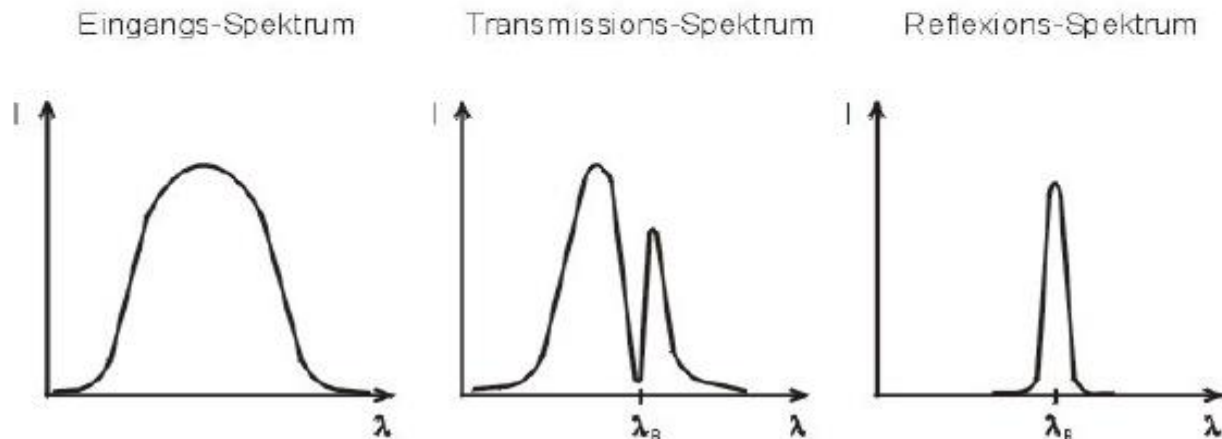
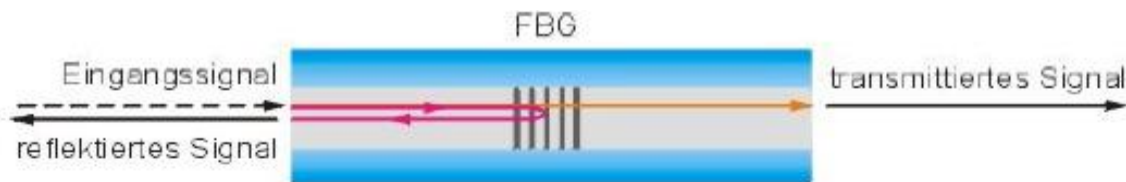
New Diagnostic Device

- Atraumatic tip (with single point sensor)
- Tension stiffening in centre of catheter (Kevlar)



Fiber Bragg Grating (FBG) Sensors

- Short optical fiber section that reflects particular wavelengths of light
- Wavelength of peaks sensitive to strain
- FBGs transduce strain to change in wavelength

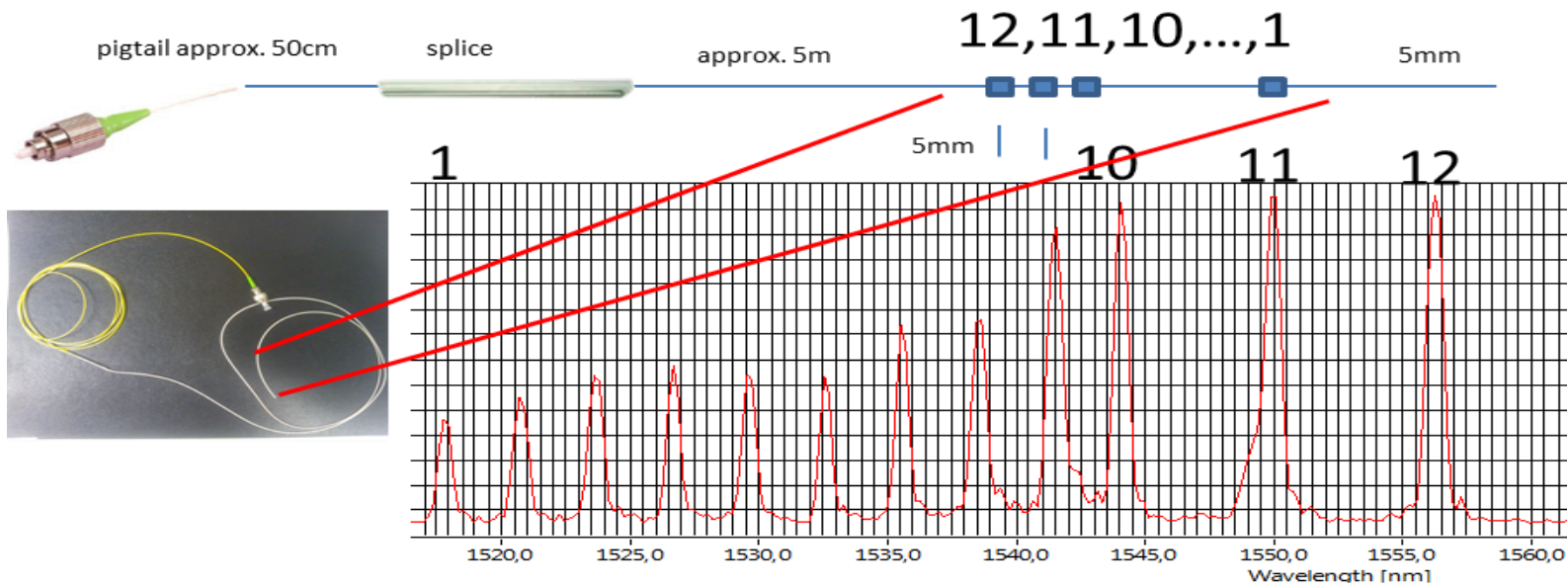
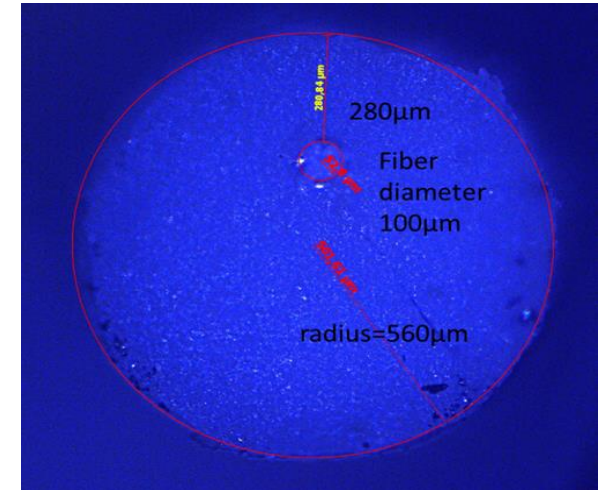


Testing in large Animal Model



Feasibility study

- Proof of concept of FBG catheters for measuring epidural pressure
- Patient undergoing spine surgery
- 1 mm diameter catheter
- 100 μ m diameter fiber

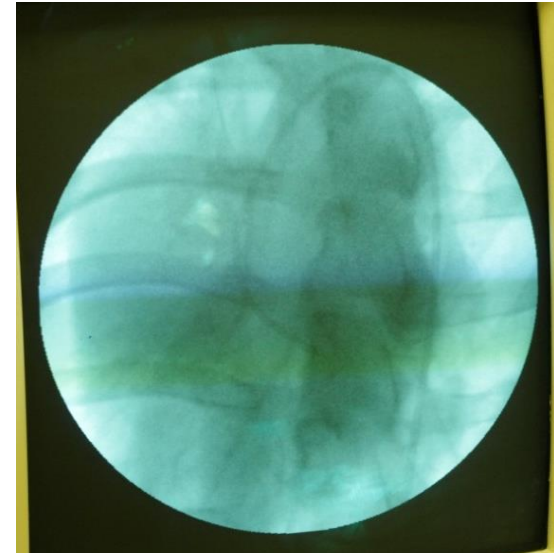
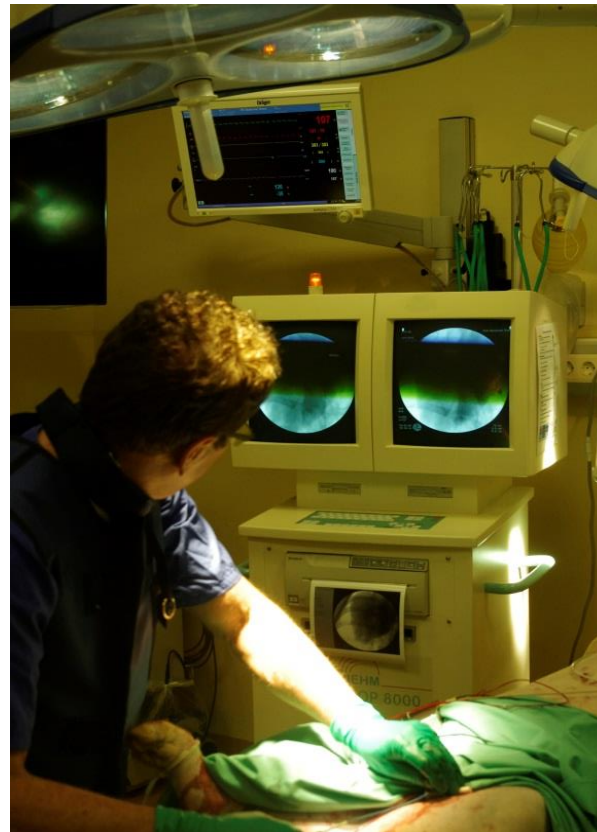


Advantages

- Real time measurement of pressure differences
 - at multiple locations
 - over long distances
 - functional measurement during workload
- Not effected by electromagnetic field
- Reducing overdiagnosis, reducing overtreatment
- Potential game changer for current medical practice in LSS

Outlook

- Knowledge transfer & exchange to / with other areas of application, (e.g. cardiology)



Delphi Approach for an Evidence-Based Diagnosis

Towards a Consensus in Screening for
Lumbar Spinal Stenosis

Defining Clinical Syndrome of LSS

Background

- LSS poorly defined clinical syndrome
- Criteria for defining a syndrome should be informed by the experience of expert clinicians

Objective

- Reach consensus among international experts on which history factors are most important in diagnosis of LSS

International Delphi Study

- International Taskforce on Diagnosis and Management of Lumbar Spinal Stenosis

Phase 1

Delphi Items

Phase 2: Round 1

Survey ISSLS Members

Phase 2: Round 2

Taskforce Item Consensus

Phase 2: Round 3

International Survey

Phase 3

Taskforce Final Consensus



Phase 1: Delphi Items

- Multidisciplinary team of 12 experts developed list of 14 clinical questions
- All questions important in diagnosis of LSS
- Consensus of 18 members of International Taskforce confirmed questions (ISSLS Scottsdale, 2013)

Phase 2: Round 1: Online Survey

1. Which factors are most important to clinicians in the diagnosis of LSS?
2. How certain are clinicians in their decisions after asking the questions?
3. How many questions are required in order to achieve reasonable diagnostic certainty?

A patient, over 65 years old, comes into your office with symptoms they attribute to the low back or leg.

You are interested in finding out if they have the clinical syndrome of lumbar spinal stenosis.

What is the first question you would ask to determine whether the patient has the clinical syndrome of lumbar spinal stenosis?

- ☐ Does the patient have thyroid disease?
- ☐ Does the patient walk WITHOUT a limp?
- ☒ Does the patient have leg or buttock pain while walking?
- ☐ Does the patient feel relief when using a shopping cart or bicycle?
- ☐ Does the patient have lower extremity weakness?
- ☐ Does the patient have diabetes mellitus?
- ☐ Does the patient have low back pain?
- ☐ Are the pulses in the foot present and symmetric?
- ☐ Does the patient flex forward to relieve symptoms?
- ☐ Does the patient have motor or sensory disturbance while walking?
- ☐ Other (specify)
- ☐ There are no additional questions, listed or unlisted, that would increase my certainty

Next >>

0% ☐ 100%



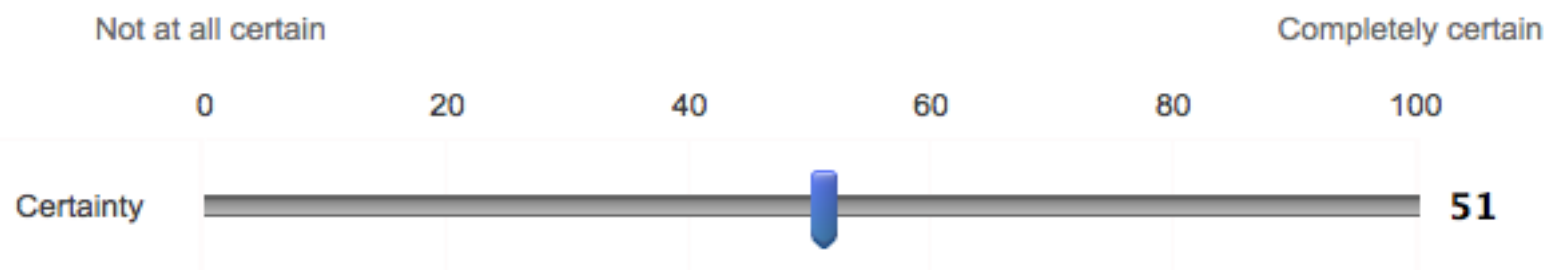
A patient, over 65 years old, comes into your office with symptoms they attribute to the low back or leg.

You are interested in finding out if they have the clinical syndrome of lumbar spinal stenosis.

What is the first question you would ask to determine whether the patient has the clinical syndrome of lumbar spinal stenosis?

- ☐ Does the patient have thyroid disease?

The patient answers "yes" to the question Does the patient flex forward to relieve symptoms?. Based on this information, how certain are you that the patient has spinal stenosis?



Next >>

0% 100%

Phase 2: Round 1

- Online survey distributed to all ISSLS members in 2013
- 68 individual responders
- 16 different countries
- Good representation by specialty

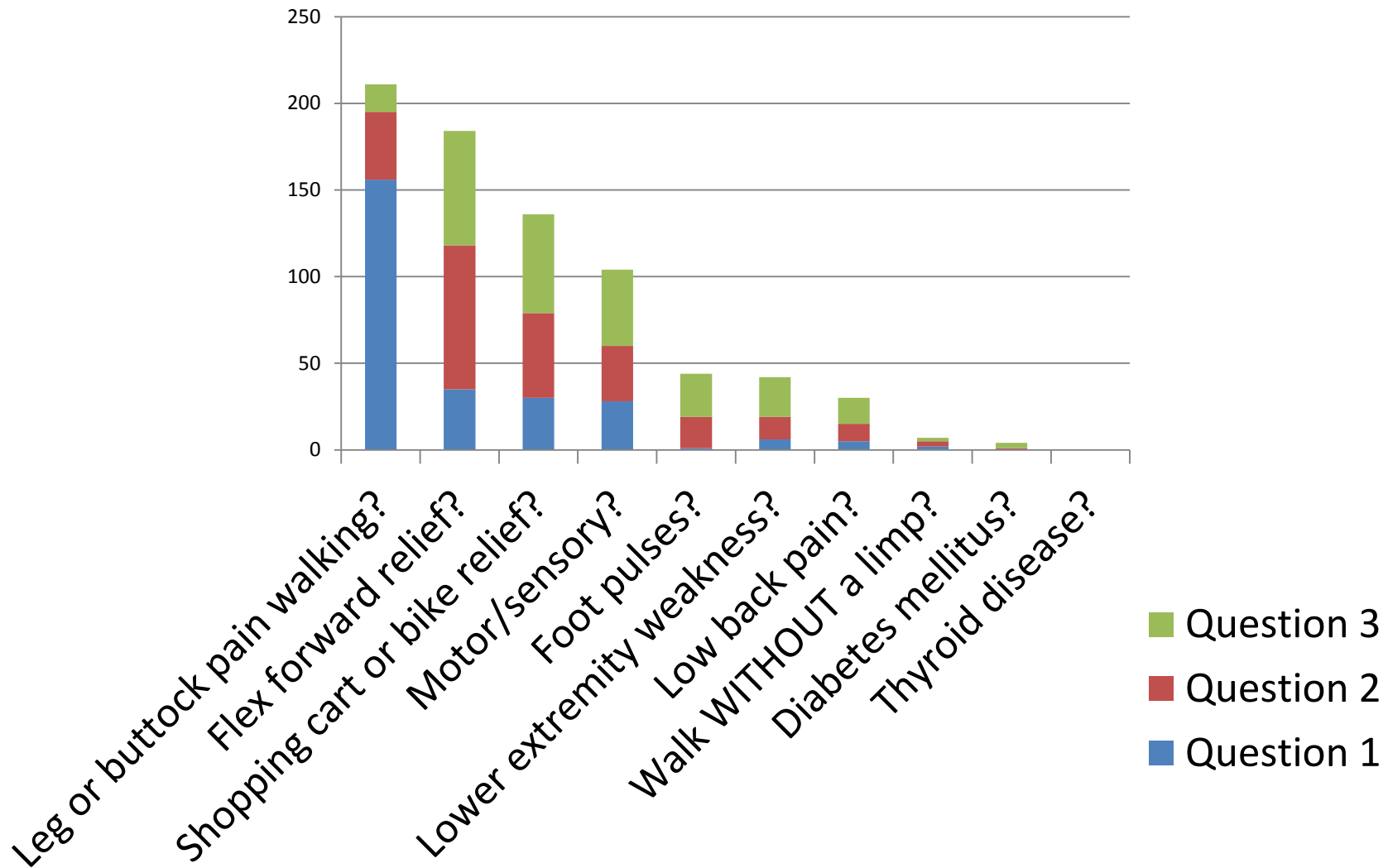
Phase 2: Round 2

- In-person meeting of 9 members of the Taskforce was conducted as a Focus Group Meeting at ISSLS Seoul, 2014
- In Round 2 consensus was reached on final list of 10 survey items

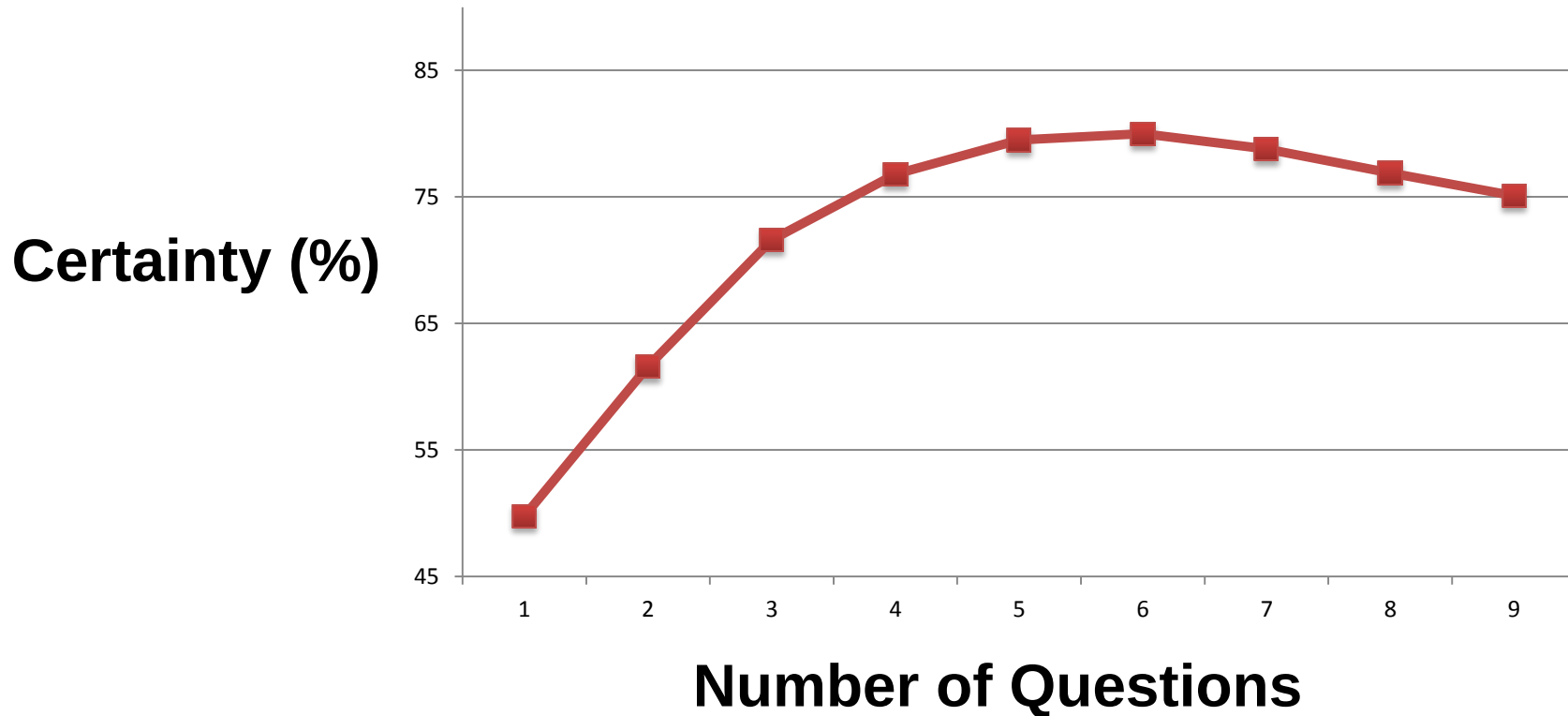
Phase 2: Round 3: Online Survey

Number of participants	279
Countries Involved (29 Unique Countries)	North America: 148 (53%) South America: 3 (1%) Europe: 67 (24%) Asia, Australia, NZ: 30 (11%) Middle East: 1 (1%)
Specialties	Orthopedics: 104 (37%) Physiatry: 87 (31%) Anesthesiology/Pain 56 (20%) Neurosurgery: 14 (5%) Primary Care: 4 (1%) Rheumatology: 3 (1%) Other: 10 (4%)
Type of practice	Private Practice: 125 (45%) Academic Institution: 125 (45%)
Years in practice	19 +/- 12

Round 3: Number of Times Asked



Changes in Certainty



** Significant ($p < 0.05$) change in certainty ceased after 6 questions at 80.0% certainty

Phase 3: Final Consensus

- 11 members of Taskforce met for final consensus (ISSLS Focus Group, June 8th, 2015)
- Final set of 6 items confirmed
- This question set provides pragmatic criterion for defining clinical LSS
- Standardization of criteria for research studies and care providers

Future Directions

- Expanding to physical exam and other diagnostic studies
- Next Delphi study to determine:
Which other diagnostic factors increase certainty of diagnosis?

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Ernst Moritz Arndt
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of ADELAIDE



The University of Hong Kong



Chiba University



Yeungnam
University



Stanford
University



Dartmouth



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University of Pittsburgh



UNIVERSITY OF
ALBERTA



UNIVERSITY OF
CALGARY



CMCC

Canadian Memorial Chiropractic College



MOUNT ROYAL
UNIVERSITY
1910

Thank You!



University of
South Australia



Neuroscience
Research Australia
Discover. Conquer. Cure.



TE WHARE WĀNANGA O TE ŪPOKO O TE IKA A MĀUI
VICTORIA
UNIVERSITY OF WELLINGTON

UNIVERSITY
of
OTAGO



Te Whare Wānanga o Ōtāgo
NEW ZEALAND

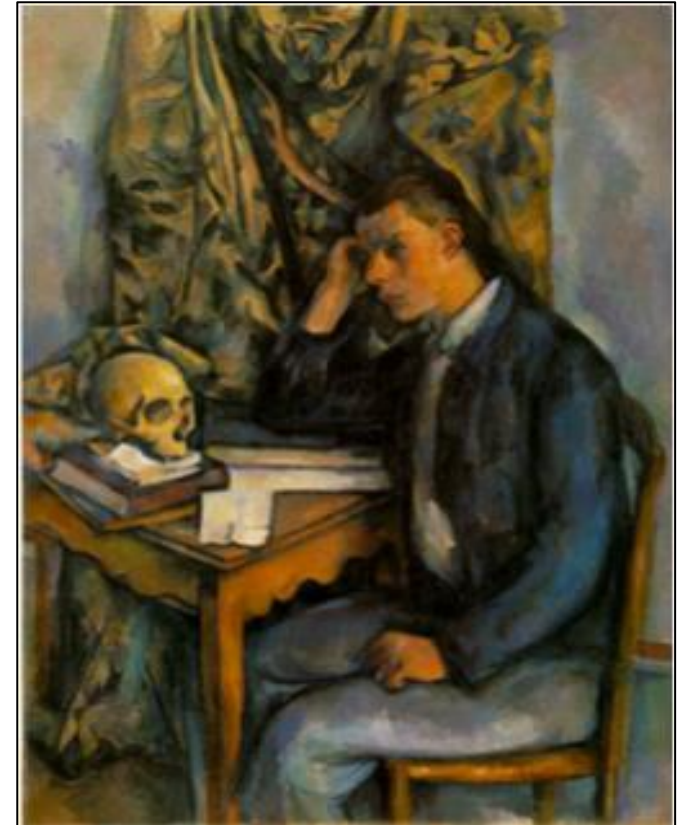


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Evolutionary Medicine: A Two Thousand Year Journey in Health Research...

Frank Rühli and team

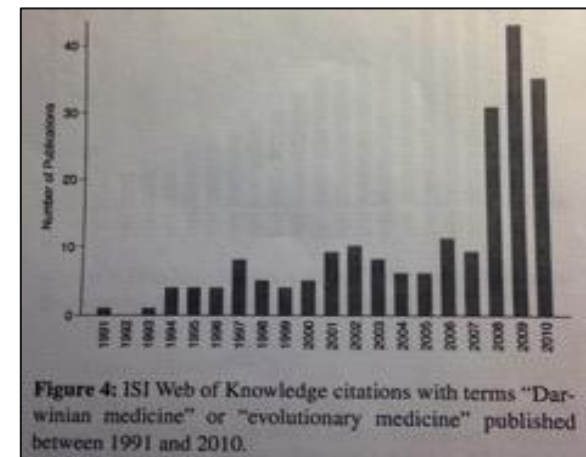


P. Cézanne, Young Man with a Skull, 1896-98



What is Evolutionary Medicine?

- Evolutionary medicine or Darwinian medicine investigates human disease vulnerability and disease aetiologies (genetics, behaviour, environment, pathogens, etc.) from evolutionary perspective.
- It also addresses future developments in human health as a result of present-day medical and socio-economic practices.
- Biomedical scientific concept since ca. the 1990s (Williams/Nesse, Q Rev Biol, 1991; Eaton et al., Am J Med, 1988).
- Humans still evolve, in terms of anatomical structures + disease patterns/prevalence.



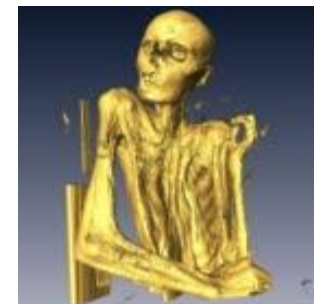
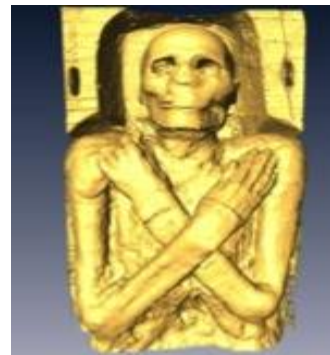
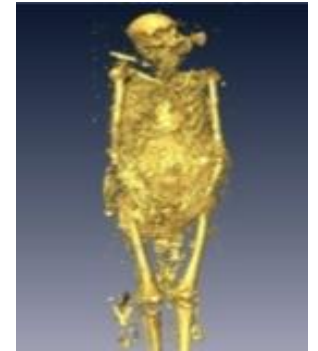
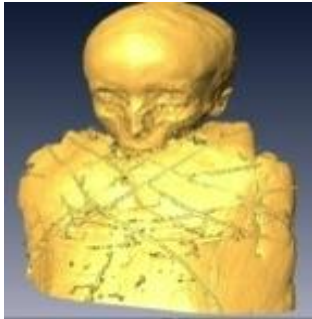


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Swiss Mummy Project www.swissmummyproject.uzh.ch

- Research Project at the University of Zürich since 1995
- MD's, Egyptologists, anthropologists, chemists, molecular biologists etc.
- Egyptian / Roman-Greek / Peruvian / Medieval / Iranian Salt Mummies / Ice Mummies etc.
- Collections in Switzerland, Germany, Italy, France, USA, Australia etc.

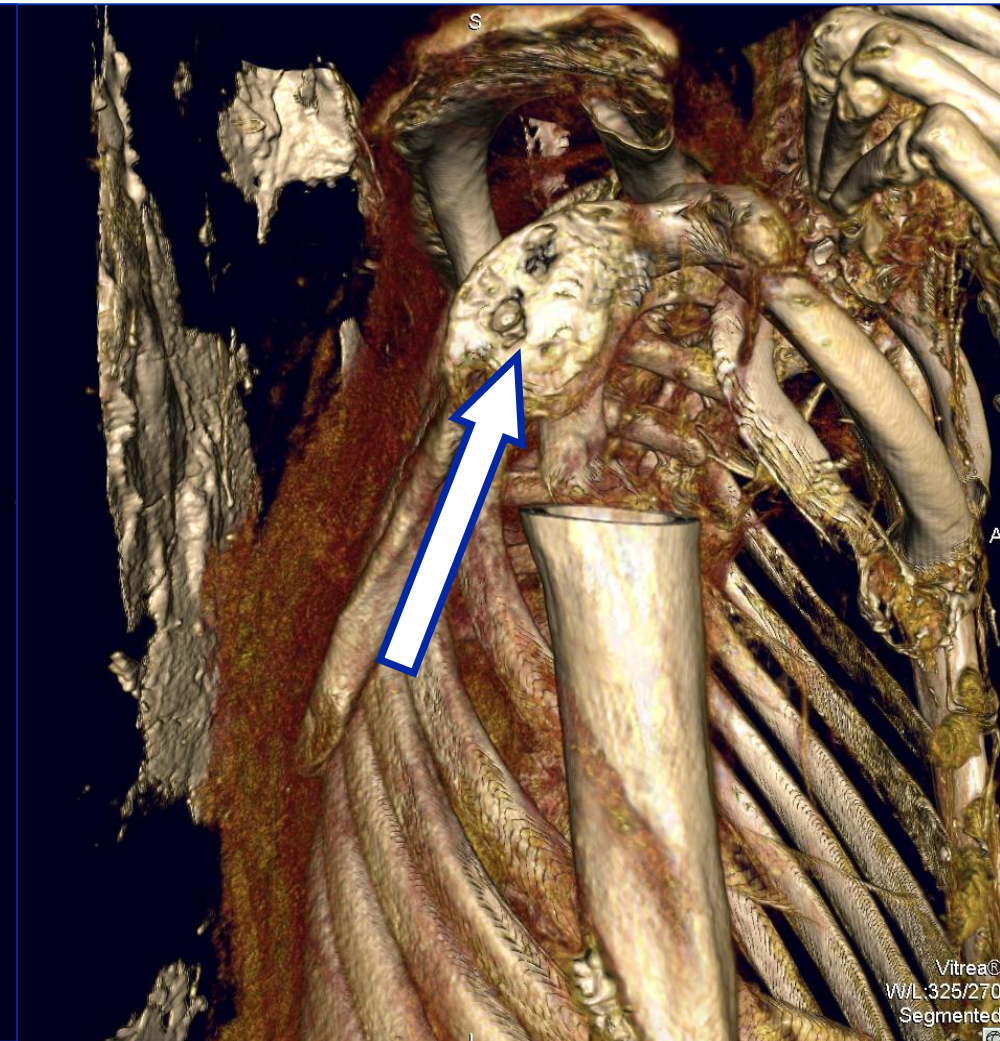
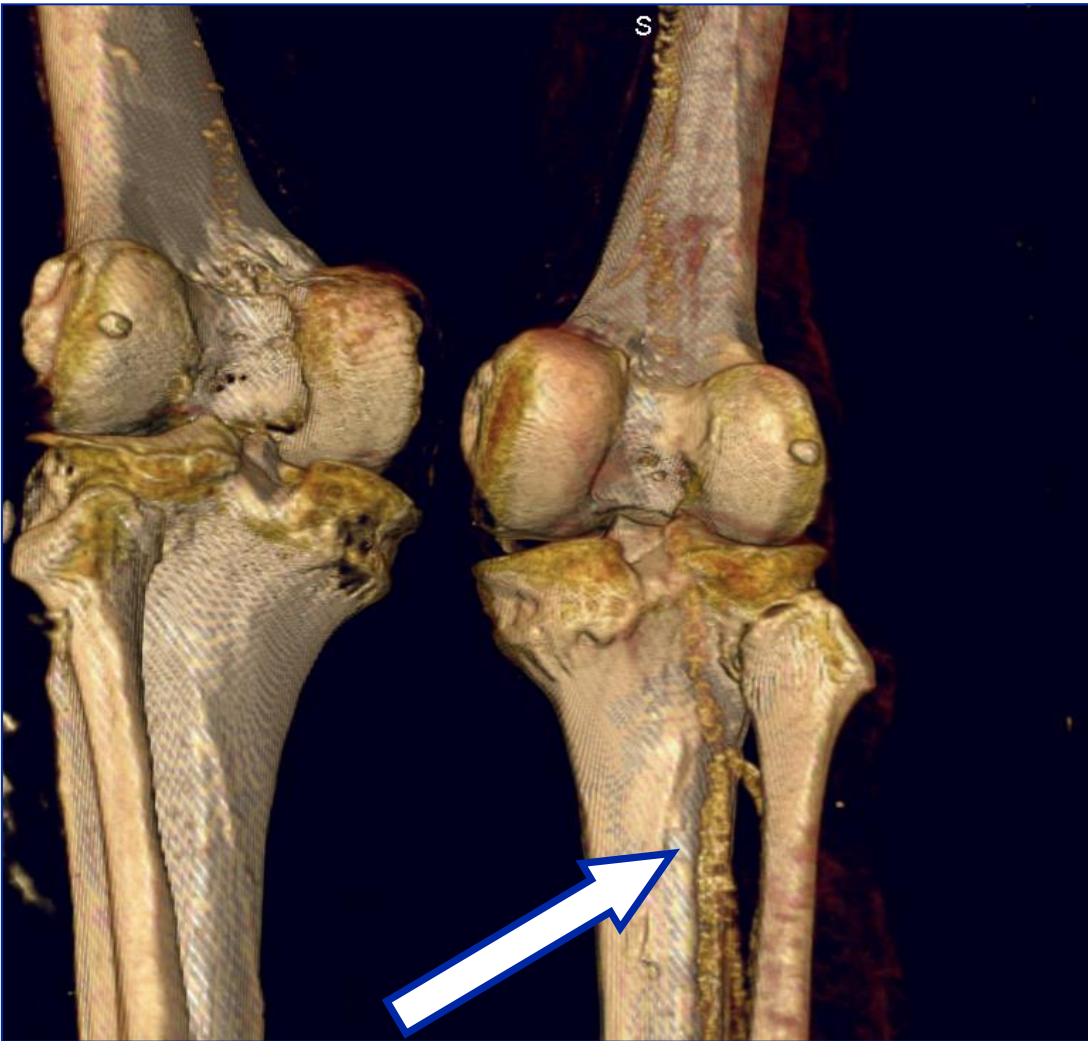




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Disease (e.g. cardiovascular / arthritis)





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Tempora mutantur...



In the past...

nowadays !





Number of mummies by time period

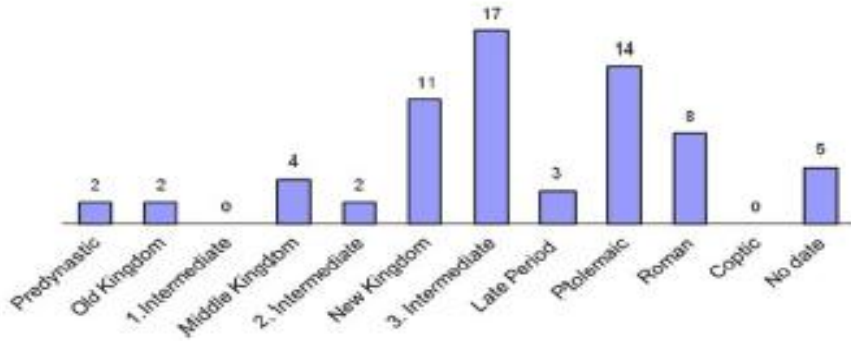


Fig. 3. Number of mummies reported by major time period ($n = 68$).

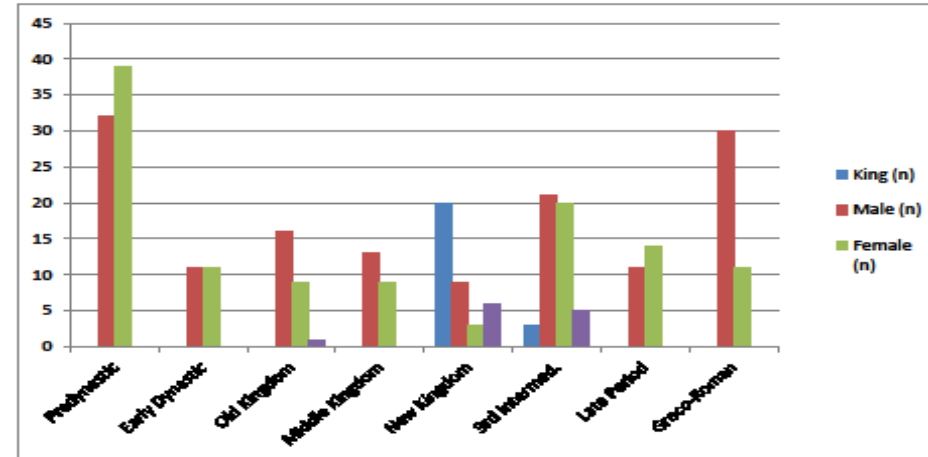
Meta-analysis

Zweifel, Böni, Rühli (J Comp Hum Biol, 2009)

N= 68

Majority:

1. 3rd Intermediate
2. Greek
3. New Kingdom



Body height study

Habicht, Henneberg, Staub, Öhrström, Rühli (Am J Phys Anthropol, 2015)

N= 259

Majority:

1. Predynastic (Skeletons)
2. Greco-Roman
3. 3rd Intermediate Period



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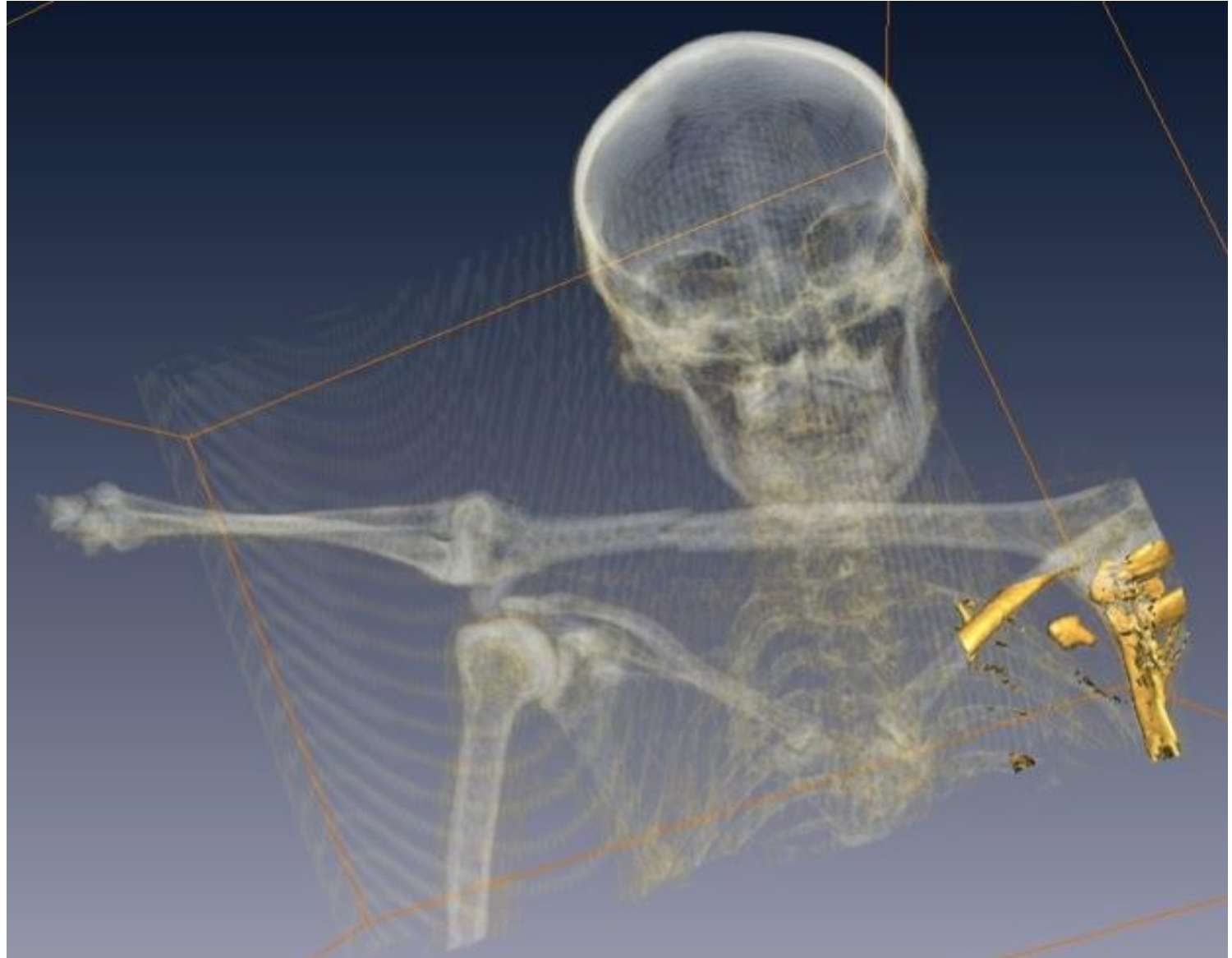
The Iceman ca. 5300 BP

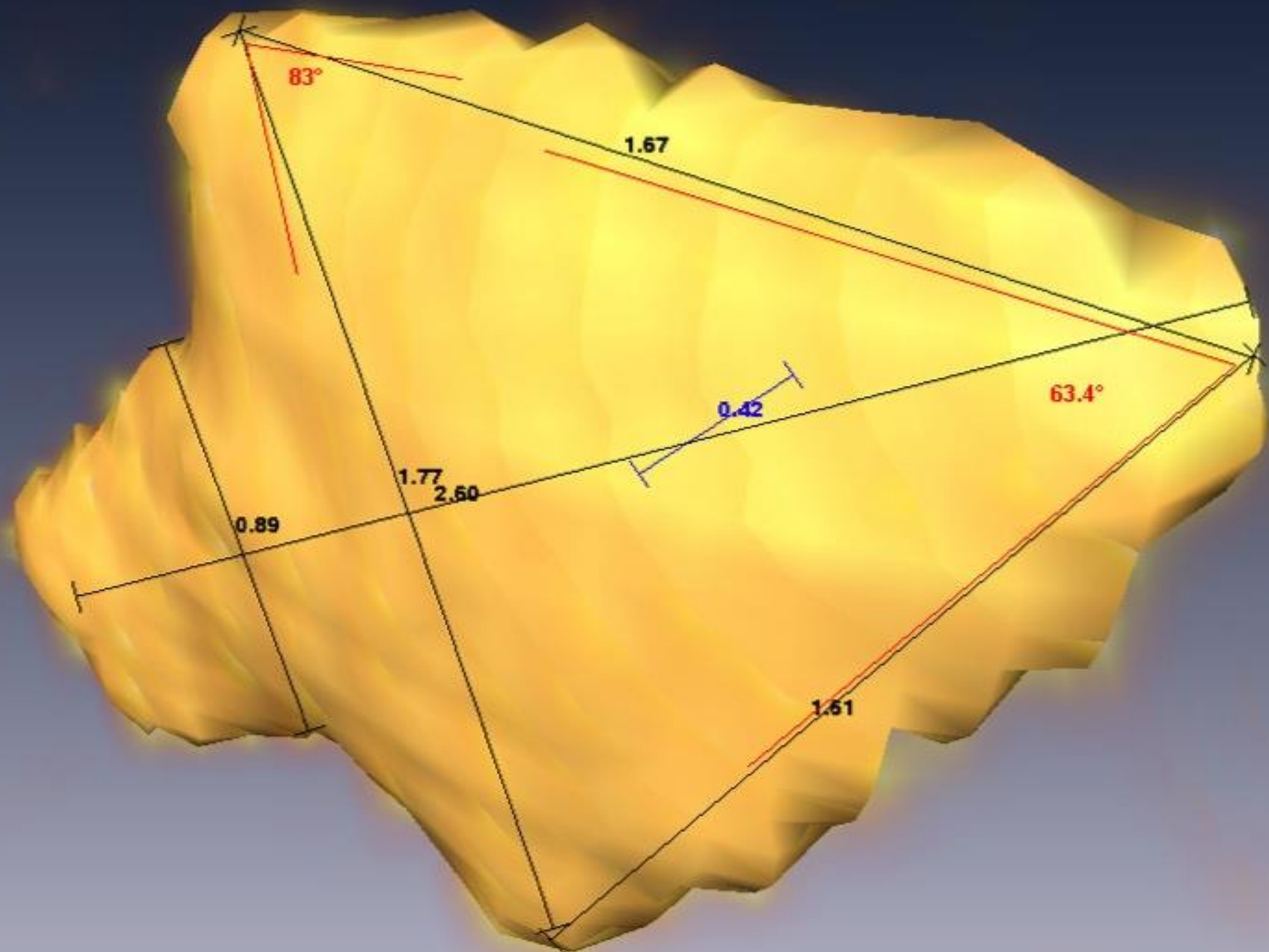




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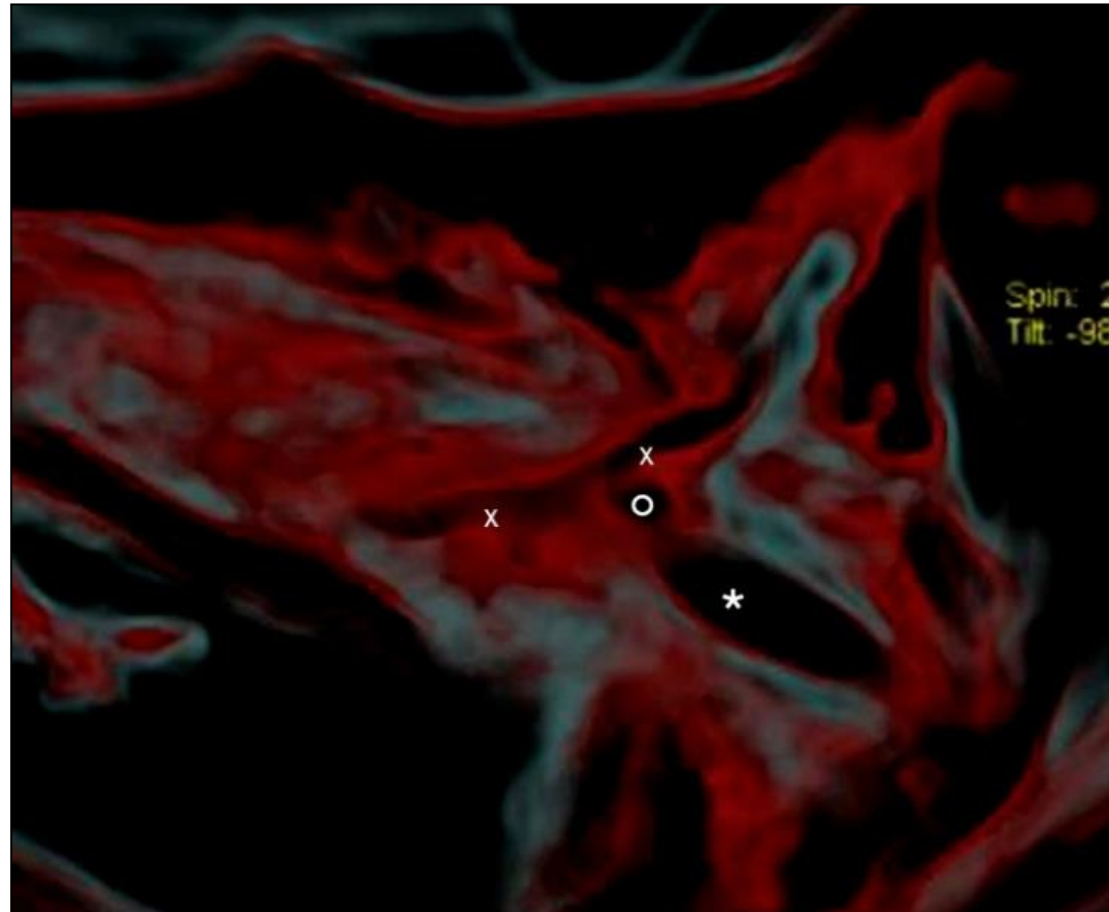
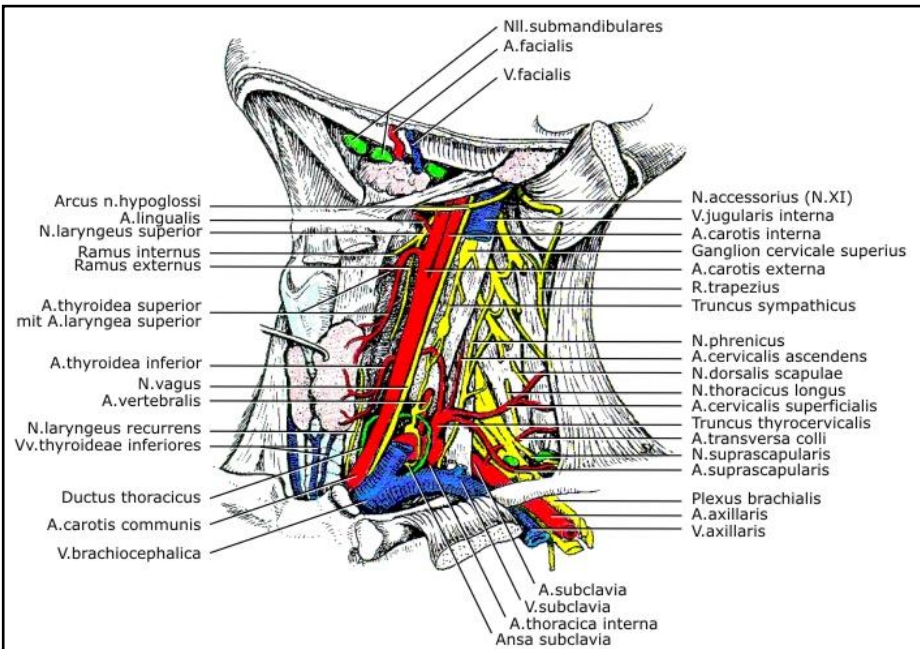


The Neolithic Iceman: Cause of death

- Laceration of subclavian artery (Pernter et al., J Archeol Sci, 2007)

- Jourdan (1820):

“...les lésions des artères placées dans l'intérieur...de la poitrine...sont essentiellement mortelles, à cause de l'hémorragie effrayante...”



Arteriosclerosis of the Iceman, ca. 5300 BP

Advanced age +

Beeing male +

Smoke +

High stress +

Periodontitis +



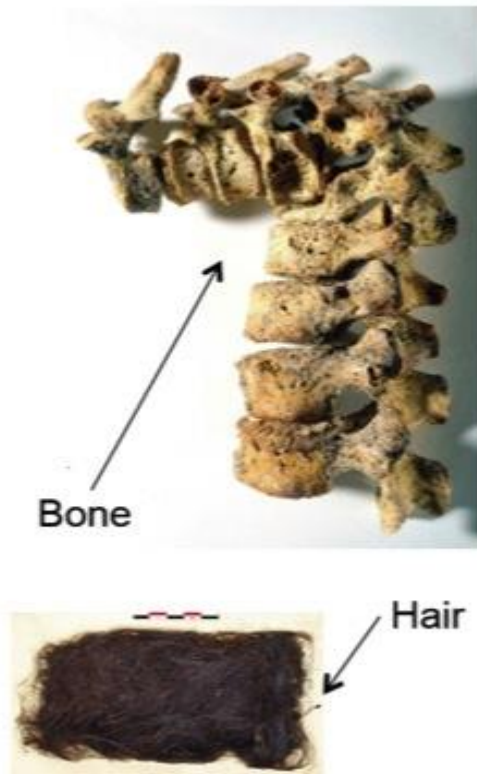
Chr.	dbSNP#	1,000 Genomes minor allele frequency	Gene	Coverage Iceman					SNP association
				A	C	G	T	N	
chr1	rs1801133	A = 0.325	<i>MTHFR</i>	10	0	1	0	0	Cardiovascular disease
chr1	rs1764391	T = 0.354	<i>GJA4</i>	0	4	0	9	0	Atherosclerosis
chr4	rs1870377	A = 0.241	<i>KDR</i>	8	0	0	9	0	Coronary heart disease
chr9	rs10757274	G = 0.396	<i>CDKNBAS</i>	1	0	8	0	0	Ischemic stroke, sudden cardiac death
chr9	rs2383206	G = 0.459	<i>CDKNBAS</i>	0	0	8	0	0	Coronary heart disease
chr13	rs5351	T = 0.436	<i>EDNRB</i>	0	14	0	20	1	Atherosclerosis
chr19	rs1613662	G = 0.141	<i>GP6</i>	4	0	3	0	0	Myocardial infarction, age

chr, chromosome; dbSNP, single nucleotide polymorphism database; SNP, single nucleotide polymorphisms.

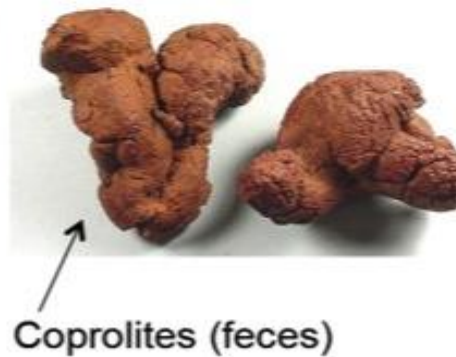




Sources of ancient biomolecules



Dental calculus Teeth



Seeds and
other botanicals



Tools



Mummified soft tissue
(skin, muscle, organs, hair)



What can we learn from ancient biomolecules?

Human ancestry and migration

Evolution of health and disease

Evolution of human diet

Origins and spread of plant and animal domestication



Proc. Natl. Acad. Sci. USA
Vol. 95, pp. 12637–12640, October 1998
Microbiology

Detection of 400-year-old *Yersinia pestis* DNA in human dental pulp: An approach to the diagnosis of ancient septicemia

(ancient DNA/paleomicrobiology/pla gene/rpoB gene)

MICHEL DRANCOURT*, GÉRARD ABOUDHARAM*, MICHEL SIGNOLI†, OLIVIER DUTOUR†, AND DEDIER RAULT*‡

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Edited by Joshua Lederberg, The Rockefeller University, New York, NY, and approved August 10, 1998 (received for review May 12, 1998)

OPEN ACCESS Freely available online



Ancient DNA Analysis Reveals High Frequency of European Lactase Persistence Allele (T-13910) in Medieval Central Europe

Annina Krüttli^{1,2,3}, Abigail Bouwman^{1,3}, Gülfirde Akgül¹, Philippe Della Casa², Frank Rühli¹, Christina Warinner^{1,3}

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Journal of Clinical Microbiology, Dec. 2002, p. 4736–4740
DOI: 10.1128/JCM.40.11.4736-4740.2002
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Vol. 40, No. 12

Detection of Mycobacterial DNA in Andean Mummies

Nami Keneni,¹ Eve Lehwelt,¹ Ken Mowbray,² Ian Tattersall,² and David Zhang^{1*}

Department of Pathology, Mount Sinai School of Medicine, New York University,¹ and American Museum of Natural History,² New York, New York

Received 20 June 2002/Returned for modification 14 July 2002/Accepted 3 September 2002



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genetics**

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NATURE GENETICS | ARTICLE

Pathogens and host immunity in the ancient human oral cavity

Christina Warinner, João F Matias Rodrigues, Rounak Vyas, Christian Trachsel, Natallia Shved, Jonas Grossmann, Anita Radini, Y Hancock, Raul Y Tito, Sarah Fiddyment, Camilla Speller, Jessica Hendy, Sophy Charlton, Hans Ulrich Luder, Domingo C Salazar-García, Elisabeth Eppler, Roger Seiler, Lars H Hansen, José Alfredo Samaniego Castruita, Simon Barkow-Oesterreicher, Kai Yik Teoh, Christian D Kelstrup, Jesper V Olsen, Paolo Nanni, Toshihisa Kawai  *et al.*

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Nature Genetics (2014) | doi:10.1038/ng.2906

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University of
Zurich^{UZH}

Institute of Evolutionary Medicine

Analysis Pipeline



DNA

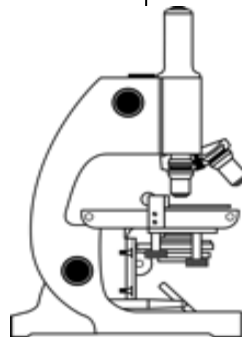
Microscopy

DNA

Proteins



Illumina HiSeq
whole genome shotgun
sequencing



Histology
Light and EM



454 GS Junior
16S gene massive parallel
sequencing



Orbitrap VELOS
whole proteome shotgun
sequencing



Results

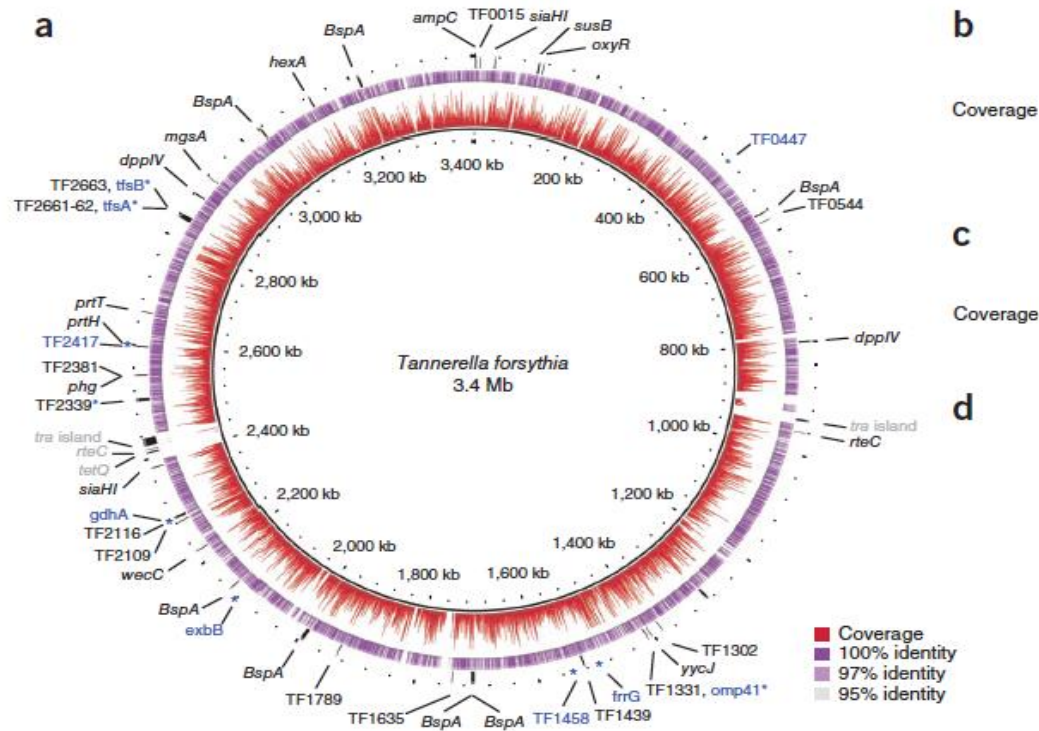


Figure 2 Genomic coverage plot for the periodontal pathogen *T. forsythia*, with details of gene a

Table 1 Putative pathogens
sequences in ancient dental

Pathogens^a

<i>Actinomyces odontolyticus</i> ^c
<i>Aggregatibacter</i>
<i>actinomycetemcomitans</i>
<i>Campylobacter concisus</i>
<i>Campylobacter curvus</i>
<i>Campylobacter rectus</i> ^c
<i>Campylobacter showae</i> ^c
<i>Capnocytophaga gingivalis</i> ^c
<i>Capnocytophaga ochracea</i>
<i>Capnocytophaga sputigena</i> ^c
<i>Clostridium difficile</i> ^{d,e}
<i>Corynebacterium matruchotii</i> ^c
<i>Eikenella corrodens</i> ^c
<i>Fusobacterium nucleatum</i>
<i>Fusobacterium periodonticum</i> ^c
<i>Gemella morbillorum</i> ^c
<i>Gordonibacter pamela</i> ^d
<i>Haemophilus influenzae</i>
<i>Histophilus somni</i> ^{d,f}
<i>Leptotrichia buccalis</i>
<i>Neisseria gonorrhoeae</i>
<i>Neisseria meningitidis</i>
<i>Neisseria sicca</i> ^c
<i>Neisseria subflava</i> ^c
<i>Porphyromonas gingivalis</i>
<i>Rothia mucilaginosa</i>
<i>Streptobacillus moniliformis</i> ^{d,f}
<i>Streptococcus agalactiae</i>
<i>Streptococcus dysgalactiae</i> ^d
<i>Streptococcus equi</i> ^{d,f}
<i>Streptococcus gallolyticus</i> ^{d,f}
<i>Streptococcus gordonii</i>
<i>Streptococcus mitis</i>
<i>Streptococcus mutans</i>
<i>Streptococcus pneumoniae</i>
<i>Streptococcus pyogenes</i>
<i>Streptococcus sanguinis</i>
<i>Streptococcus suis</i> ^{d,f}
<i>Tannerella forsythia</i>
<i>Treponema denticola</i>
<i>Veillonella parvula</i>



Micro-evolutionary changes of the skeletal system

- Changes in prevalence
 - Tarsal coalitions
 - Ossification of the posterior longitudinal ligament (Hukuda et al. 2000)
 - Diffuse idiopathic skeletal hyperostosis (Arriaza, 1993)
 - Hyperostosis frontalis interna (Rühli and Henneberg, 2004, 2005)

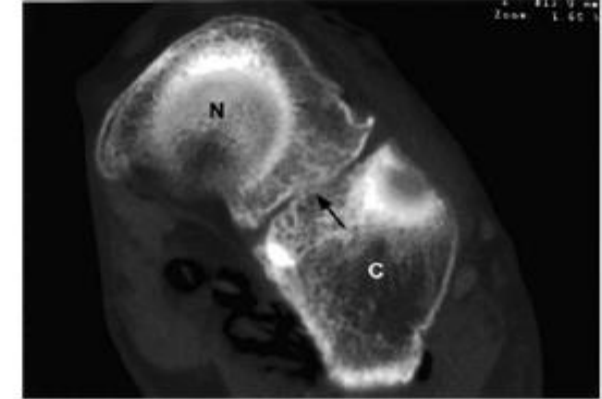


Fig. 5. Specimen 71. Calcaneonavicular coalition (arrow) confirmed by dissection.

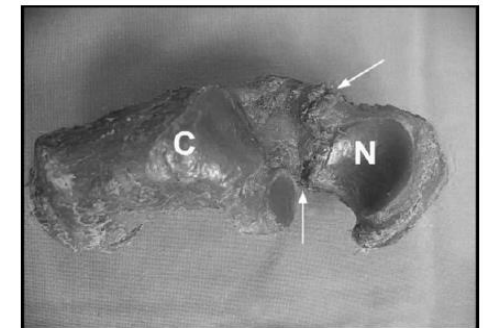


Fig. 1. Calcaneonavicular coalition (no. 71): C, calcaneus; N, navicular; arrows, calcaneonavicular coalition.

Clinical Anatomy 16:411–415 (2003)

ORIGINAL COMMUNICATION

High Prevalence of Tarsal Coalitions and Tarsal Joint Variants in a Recent Cadaver Sample and Its Possible Significance

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A dissection and computer tomograph study of tarsal coalitions in 100 cadaver feet

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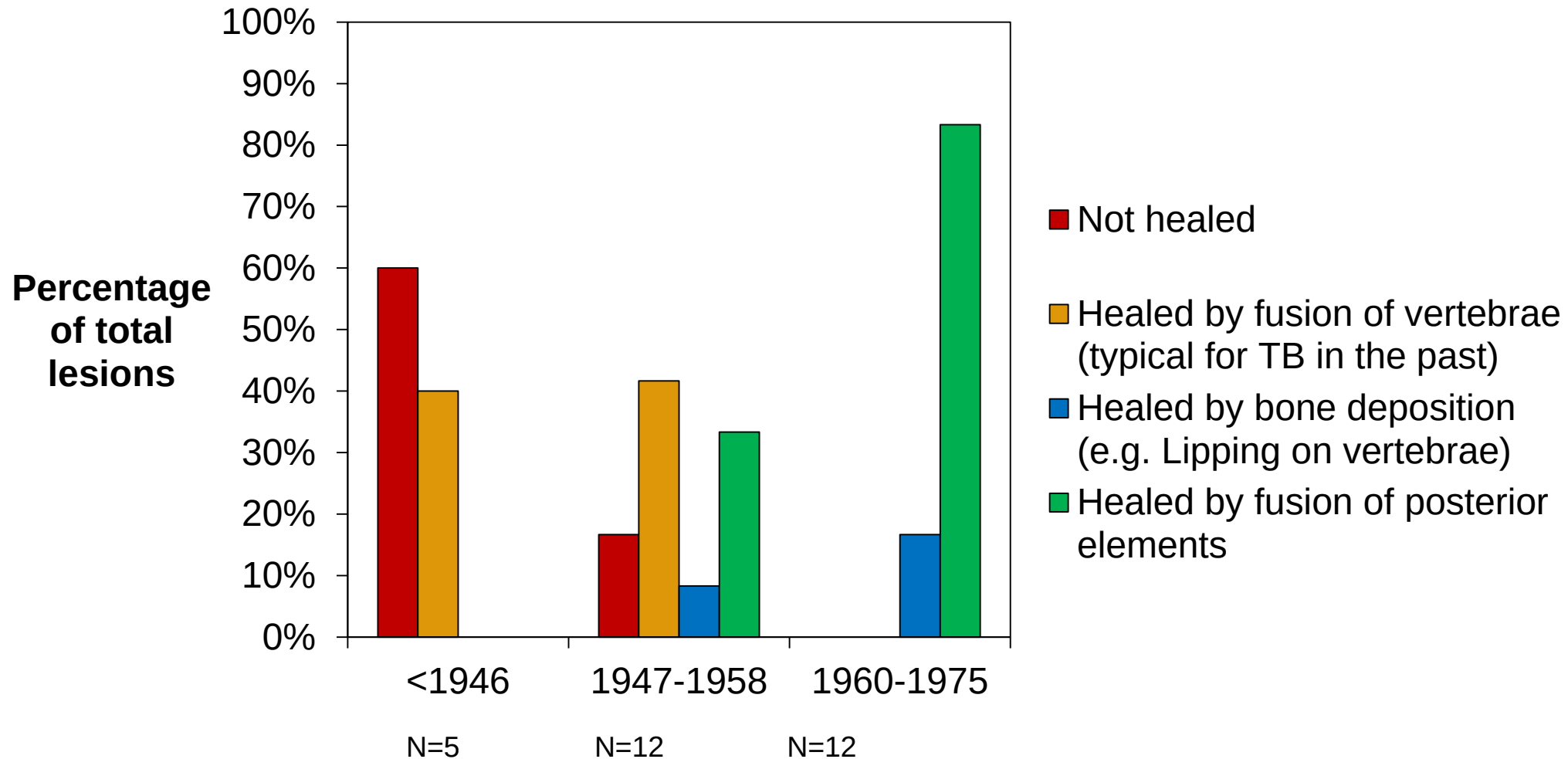
Received 28 September 2001; accepted 21 July 2002

TABLE 2. Reported Prevalence of Tarsal Coalitions in Adults

Prevalence	Sample	Method	Reference
0.03% (1/3,600)	Conscripts (asymptomatic?)	Physical examination and x-ray (?)	Harris and Beath, 1948
1.05% (21/≈2,000)	Army hospital patients	Physical examination and x-ray	Vaughan and Segal, 1953
2.50% (21/840)	Cadavers	Dissection	Pfizzner, 1896
12.90% (8/62)	Cadavers	Dissection	Current study



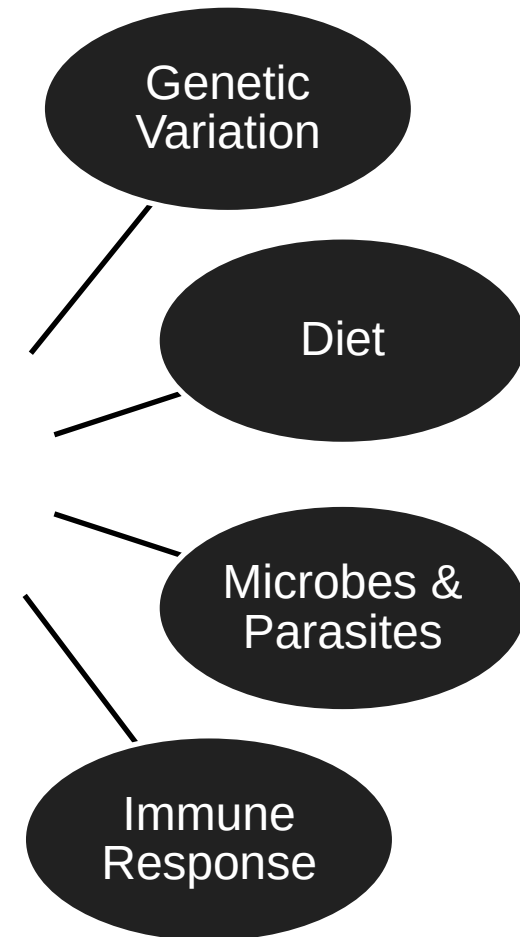
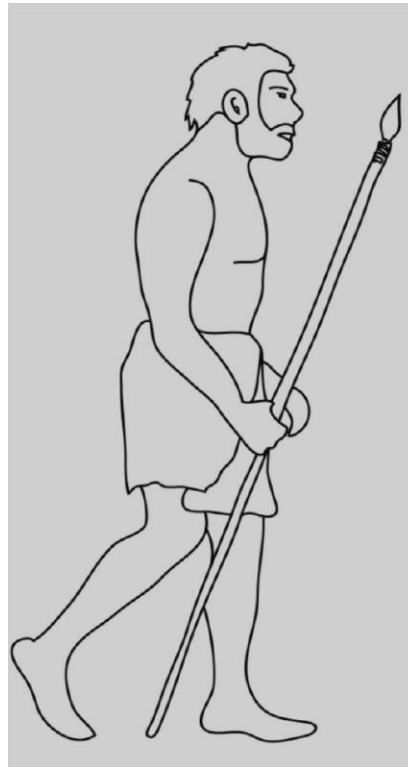
Skeletal Lesion Healing Through Time (Holloway et al., 2013)





Outlook: Disease and evolutionary etiologies

Allergies
Atherosclerosis
Celiac Disease
Obesity
Meningitis
Periodontitis
Type II Diabetes





What have we done to us ?

Insulated our bodies from climate (shelter and clothing, heating and cooling, sunshades etc.)

Produced our food (basic foodstuffs, fermentation, additives, vitamins etc.)

Removed parasites

Repaired our bodies (prosthetics, cleaning)

Increased our physical performance (tools, lifts, cars, airplanes, binoculars, microscopes, weapons)



Benefits of evolutionary medicine

- Evolutionary medicine offers us a new perception of the human body
- It is wrong to believe that evolution is a thing of the past and that a *Homo sapiens*, once formed, remains the same biological entity throughout the centuries.
- One of the most useful generalizations evolution offers to medicine is a vision of the body as a bundle of trade-offs.
- No trait is perfect. Every trait could be better, but making it better would make something else worse.



Impact – what is normal?

- A “**morphological anomaly**” may become more frequent or even “**normal**” in a given population and, thus, it shall be no reason for concern for a particular individual.
- This needs to be realized and communicated accordingly e.g. by general practitioners to their patients.
- **Accepting variation as normal is an important issue in clinical medicine.**



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www.iem.uzh.ch

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