Musing on multidisciplinary diagnosis

San Francisco June 2015

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Royal Brompton Hospital, London, UK

New extension building of Brompton Hospital, built in 1882

cc
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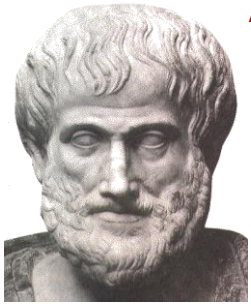
AUW has received consultancy or lecturing fees from Actelion, Bayer, Boehringer Ingelheim, Centricorp, Chiesi, Genentech, Gilead, Intermune, Medimmune, Novartis, Takeda

Musings……

- A philosophical basis
- The MD ethos: how pathologists think?
- MD diagnosis and IPF guidelines
- HP and unclassifiable disease
- An ERS Task Force view
- Personality and MD diagnosis
- MD diagnosis: a potent research tool

Views of perception

- The universe as a sea
- The Aristotelian view: what matters is observing the waves and deducing what lies below the surface
- The Platonic view: what matters is the depths below the surface: do not be seduced by the waves



Aristotle: the father of science

Observe

Compare

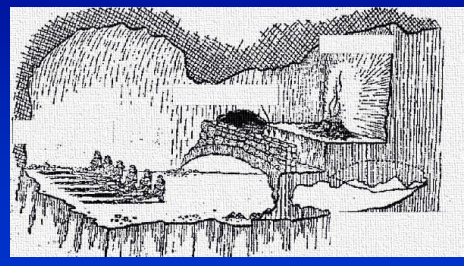
Hypothesize

Plato: the mystic

or is that really so?

Plato: the theory of forms

- There exists an ideal world with an ideal cat and an ideal dog…
- This ideal world casts "shadows" and what we perceive in the material world are shadows of the ideal world



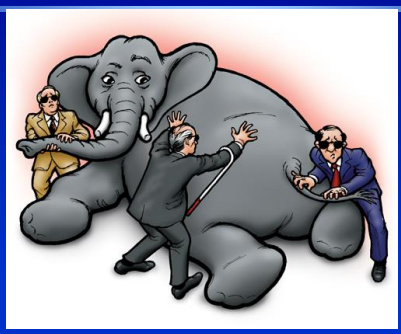
Plato's ideal world does not exist

But in science, things that do not exist may be essential concepts ……..

The theory of forms

- In diffuse lung disease, we search for an ideal statement of the essence of disease
- All statements are imperfect
- We have shadows.

Multidisciplinary diagnosis

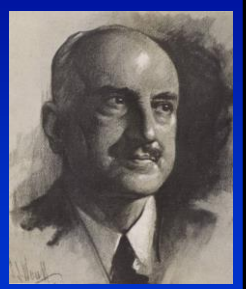


Why histological evaluation is a shadow and not a diagnostic gold standard…….

George Santayana (1863-1952)

"Those who cannot remember the past are condemned to repeat it"

"Those who forget the errors of history are doomed to repeat them"



How this might play out in IPF

- **In 1999, IPF was viewed as a single disease**
- **In 2015, IPF is viewed as a single disease**
- **But it was not the same disease: histo-pathologists had defined NSIP and this entity made clinical and radiologic sense**
- **In 2029, we will still have a disease called IPF but it will be a different disease**

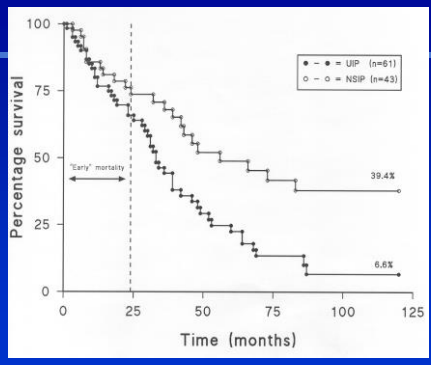
But given this constraint, can we view histopathology from a surgical biopsy as a diagnostic gold standard on other grounds?

Essentially, there are no diagnostic gold standards in interstitial lung disease: biopsy is merely the most argentiferous of a number of diagnostic silver standards

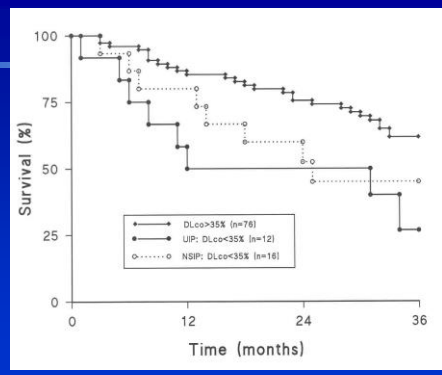
Biopsy in severe disease

- **Risk/benefit ratio**
- **Risk increases as gas transfer falls below 30-35%**
- **Prognostic value diminishes as gas transfer falls below 30-35%%**

The clinical entity of "IPF": histologic patterns



Latsi PI et al, Am J Respir Crit Care Med, 2003.



Sampling error

- UIP/NSIP: heterogeneity between biopsies
- Large cohort of IPF/NSIP cases with two biopsies
- 50% concordant UIP; 25% concordant NSIP; 25% discordant
- Discordant cases had the outcome of UIP
- RBH data broadly compatible

Flaherty KR et al. AJRCCM 2001; 164:1722-1727

Variation between pathologists

- At the time of the Nicholson 2004 study, a curious paucity of ILD studies
- This probably reflected a wish by all to view histology as a security blanket
- The paper had a very mixed reception at review but eventually found a home in *Thorax*
- 133 biopsies scored in 97 patients

Nicholson AG et al, Thorax 2004; 59:500-505

Permitted histopathological patterns

1 Usual interstitial pneumonia
2 Non-specific interstitial pneumonia (A or B)
3 Desquamative interstitial pneumonia
4 Respiratory bronchiolitis
5 Diffuse alveolar damage
6 Organising pneumonia
7 Lymphocytic interstitial pneumonia
8 Follicular bronchiolitis
9 Hypersensitivity pneumonitis
10 Sarcoidosis
11 Non-diagnostic
12 Within normal limits
13 Other
14 End stage lung
15 Unclassifiable

Nicholson AG et al, Thorax 2004; 59:500-505

"Ennumerating how pathologists think……"

1	NK			2B	2	2B(85) 1(15)
	NK			2B	3	2B(50) 1(10) 11(40)
2	RLL			1	1	1(100)
	RUL			2B	3	2B(60) 1(40)
3	RLL			4	3	4(50) 11(50)
	RUL			4	3	4(50) 11(50)
4	NK			1	1	1(100)
5	LLL			9	2	9(70) 2A(20) 6(10)
	LUL			2A	3	2A(50) 9(50)
6	RLL			9	3	9(60) Bronchiolitis (40)
	RUL			1	3	1(50) 9(50)
7	RML			9	3	9(60) 2B(30) 3(10)
	RLL			2B	2	2B(70) 1(30)
8	LLL			9	1	9(95) 10(5)
	LUL			9	1	9(95) 10(5)

Nicholson AG et al, Thorax 2004; 59:500-505

Inter-observer agreement: 10 regional UK pathologists

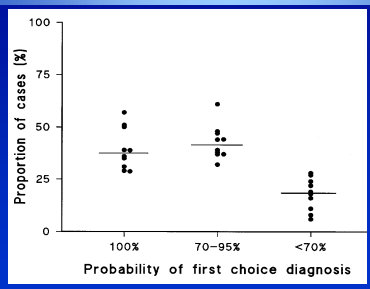
- First choice diagnosis **k = 0.38**
- When diagnosis confident **k = 0.50**
- When diagnosis not confident **k = 0.22**
- Note: these are pathologists with an ***interest*** in DILD

Nicholson AG et al, Thorax 2004; 59:500-505

These results are better than might appear

- **Often, patterns are a very close call: two pathologists should expect to disagree when likelihoods are close to 50/50**
- **Confidence increases agreement and can be stated by the pathologist**
- **At that time, people were still coming to terms with the entity of NSIP ("*Nobody Said It's Perfect*")**

Nonetheless…..the problem of indeterminate appearances



Nicholson AG et al, Thorax 2004; 59:500-505

Biopsy alone was patently insufficient in many cases…….

Historical approaches to diagnosis

- **Biopsy all patients: therein lies diagnostic truth. Clinical reasoning has no role**
- **View all IIP as essentially the same disorder: "cyptogenic fibrosing alveolitis". Clinical reasoning has no role.**
- **HRCT provides "truth data". Clinical reasoning has no role**

"Old classifications never die: only the people that use them do"

HISTOLOGIC PATTERNS	CLINICAL DIAGNOSIS
UIP	Idiopathic Pulmonary Fibrosis Cryptogenic Fibrosing Alveolitis
DIP (Alveolar Macrophage Pneumonia)	DIP (Alveolar Macrophage Pneumonia)
Respiratory Bronchiolitis (RB)	Respiratory Bronchiolitis Interstitial Lung Disease (RBILD)
Organizing Pneumonia (OP)	Cryptogenic organizing Pneumonia (*BOOP)
Diffuse Alveolar Damage (DAD)	Acute Interstitial Pneumonia (AIP)
Non-Specific Interstitial Pneumonia (NSIP)	*Non-Specific Interstitial Pneumonia (**Provisional)*
Lymphoid Interstitial Pneumonia (LIP)	Lymphoid Interstitial Pneumonia

2002

CATEGORY	CLINICAL-RADIOLOGIC-PATHOLOGIC DIAGNOSES	ASSOCIATED MORPHOLOGIC PATTERNS
Chronic Fibrosing IP	Idiopathic Pulmonary Fibrosis	Usual Interstitial Pneumonia
	Idiopathic Nonspecific Interstitial Pneumonia‡	Nonspecific Interstitial Pneumonia
Smoking-related IP †	Respiratory Bronchiolitis Interstitial Lung Disease	Respiratory Bronchiolitis
	Desquamative Interstitial Pneumonia	Desquamative Interstitial Pneumonia
Acute/subacute IP	Cryptogenic Organizing Pneumonia	Organizing Pneumonia
	Acute Interstitial Pneumonia	Diffuse Alveolar Damage

2013

Another approach to diagnosis…

The goal of IPF guidelines is to allow less expert doctors to achieve optimal outcomes based on a secure diagnosis

In the current model, so-called multidisciplinary diagnosis is wholly in the hands of non-clinicians

HRCT Pattern	Surgical Lung Biopsy Pattern (when performed)	Diagnosis of IPF?
UIP	UIP Probable UIP Possible UIP Non-classifiable fibrosis	YES
	Not UIP	No
Consistent with UIP	UIP Probable UIP	YES
	Possible UIP Non-classifiable fibrosis	Probable
	Not UIP	No
Inconsistent with UIP	UIP	Possible
	Probable UIP Possible UIP Non-classifiable fibrosis Not UIP	No

Raghu G, Collard HR, Egan JJ, et al. Am J Respir Crit Care Med 2011;183:788-824.

Clinical reasoning has no role

American Thoracic Society Documents

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

Ganesh Raghu, Harold R. Collard, Jim J. Egan, Fernando J. Martinez, Juergen Behr, Kevin K. Brown, Thomas V. Colby, Jean-François Cordier, Kevin R. Flaherty, Joseph A. Lasky, David A. Lynch, Jay H. Ryu, Jeffrey J. Swigris, Athol U. Wells, Julio Ancochea, Demosthenes Bouros, Carlos Carvalho, Ulrich Costabel, Masahito Ebina, David M. Hansell, Takeshi Johkoh, Dong Soon Kim, Talmadge E. King, Jr., Yasuhiro Kondoh, Jeffrey Myers, Nestor L. Müller, Andrew G. Nicholson, Luca Richeldi, Moisés Selman, Rosalind F. Dudden, Barbara S. Griss, Shandra L. Protzko, and Holger J. Schünemann, on behalf of the ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis

This Official Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS), the Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) Was Approved by the ATS Board of Directors, November 2010, the ERS Executive Committee, September 2010, the JRS Board of Directors, December 2010, and the ALAT Executive Committee, November 2010

This Statement has been formally endorsed by the Society of Thoracic Radiology and by the Pulmonary Pathology Society

Am J Respir Crit Care Med 2011; 183: 788

The guidelines are now broken because ……..

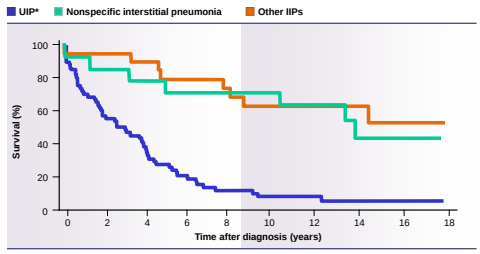
This house is in favour of treating patients with probable/possible IPF

Athol Wells

versus

Paul Bresser

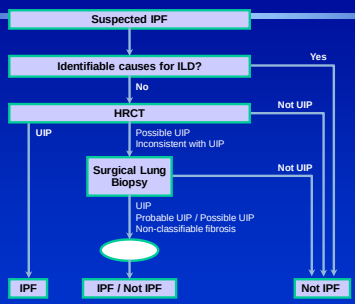
IIP: *diagnosis is prognosis*



*UIP is the defining histological pattern of IPF.

Bjoraker JA, Ryu JH, Edwin MK, et al. Am J Respir Crit Care Med 1998;157:199-203.

IPF Diagnostic Algorithm



Adapted from: Raghu G, Collard HR, Egan JJ, et al. Am J Respir Crit Care Med 2011;183:788-824.

This is "multidisciplinary diagnosis"?!?!?

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Consistent with UIP	UIP Probable UIP	YES
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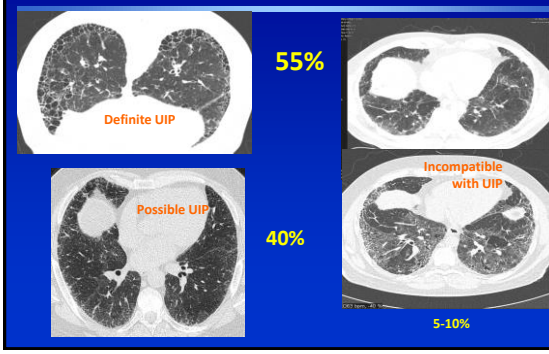
	Not UIP	No
Inconsistent with UIP	UIP	Possible
	Probable UIP Possible UIP Non-classifiable fibrosis Not UIP	No

In IPF, guidelines work if the answer to one of these questions is "yes"

- Can IPF be diagnosed using HRCT in almost all cases?
- If not, is a biopsy diagnosis in virtually all cases realistic when HRCT fails?
- If not, is the same broad management appropriate for all realistic differential diagnoses?

The CT spectrum of IPF



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Contraindications to biopsy

Severity

Age

Comorbidity

Lack of timely access

Patient disinclination

The ATS/ERS/JRS/ALAT recommendation to biopsy "possible UIP" can be carried out in perhaps 15% of cases

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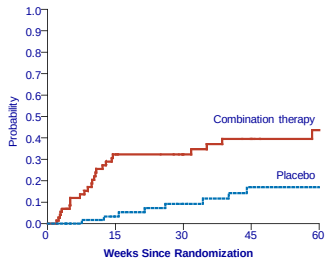
Does the same treatment approach work for IPF, NSIP and chronic HP?

- Before the PANTHER study, the answer was "yes"
- Triple therapy seemed to be broadly reasonable for all three diagnoses
- The guideline worked OK in clinical practice
- Commendable rigour in IPF diagnosis for trial purposes

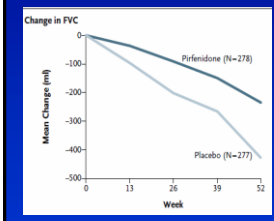
Time to Death or Hospitalization

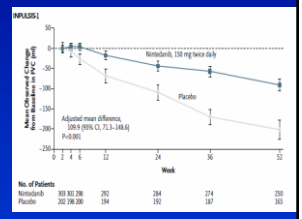


No. at Risk					
Combination therapy	77	40	29	23	10
Placebo	78	55	42	26	16

Raghu G et al. N Engl J Med 2012; 366:1968-77.

For the first time, diagnosis really mattered





The ATS/ERS diagnostic guideline in 2015

40-50% of IPF patients have unclassifiable disease

In these patients, clinicians now have to guess whether to manage as for IPF or for the alternative diagnoses

The solution is clinical reasoning

IPF diagnoses for drug trials requires standardised data and the exclusion of all information that is not available in all cases i.e. HRCT dominates

By contrast, IPF diagnoses in clinical practice require the integration of all available data in every individual

Therefore, the designation of possible/ probable IPF from guidelines does not capture possibilities and probabilities in clinical practice.

Background to an ERS Task Force

- Our goal should be to reach a "working diagnosis of IPF" by the use of logic and review of all data in a multidisciplinary setting
- Rigid diagnostic criteria cannot work because the permutations of available data are vast
- We can, however, define the data set that should ideally be considered

"A working diagnosis of IPF"

- That level of diagnostic likelihood such that in an individual case, IPF-specific therapy is the only logical intervention
- In fact, all "definite" IPF diagnoses are, in reality, working diagnoses and so are many "probable" IPF diagnoses.
- A rigid view of when IPF is "definite" and when IPF is "very probable" may not help us

A working multidisciplinary diagnosis of IPF

- BAL and disease behaviour should influence making a working diagnosis of IPF
- HRCT should no longer occupy the central diagnostic ground
- Instead: three multidisciplinary algorithms with HRCT as the starting point of each pathway and a minimum data set defined

How often does CHP mimic IPF?

In current guidelines, a typical UIP pattern on HRCT equates to IPF in the correct clinical context

•Series in which consecutive patients diagnosed with IPF, meeting ATS/ERS criteria, were reviewed

•Critical evaluation of possible occult HP based upon antigen positivity, bronchial provocation testing and review of biopsy

Morell F et al, Lancet Respir Med 2013, 1:685-94

Methods In this case-cohort study, 60 consecutive patients diagnosed with IPF on the basis of the 2000 American Thoracic Society (ATS) and the European Respiratory Society (ERS) criteria were prospectively followed up every 4 months for 6 years between Jan 1, 2004, and Dec 31, 2009. At each visit a uniformly applied questionnaire was administered to these 60 patients to identify occult antigen exposure known to cause hypersensitivity pneumonitis. Patients underwent specific IgG determination, bronchoalveolar lavage, bronchial challenge testing with suspected antigens, and re-review of histopathological features in existing and subsequently obtained surgical lung biopsy samples and from lung explants. Specimens obtained from suspected sources from the patient's environment were

Interpretation Almost half of patients diagnosed with IPF on the basis of 2011 criteria were subsequently diagnosed with chronic hypersensitivity pneumonitis, and most of these cases were attributed to exposure of occult avian antigens from commonly used feather bedding. Our results reflect findings in one centre with recognised expertise in chronic hypersensitivity pneumonitis, and further research and studies at other centres are warranted.

Panel 1: Diagnostic criteria for chronic hypersensitivity pneumonitis

Chronic hypersensitivity pneumonitis can be diagnosed in patients with clinical and high-resolution CT findings of usual interstitial pneumonia or idiopathic pulmonary fibrosis meeting any one of the following three criteria:

- Positive bronchial challenge testing (this criterion is reinforced by often coinciding with positivity of specific IgG).
- Specific IgG positivity and surgical lung biopsy sample compatible with hypersensitivity pneumonitis or greater than 20% lymphocytes in bronchoalveolar lavage specimen (>20% lymphocytes is seen in 85% of patients with chronic hypersensitivity pneumonitis;[15] see Discussion).
- Surgical lung biopsy sample or explanted lung showing histopathological features or characteristics of subacute hypersensitivity pneumonitis (see below).

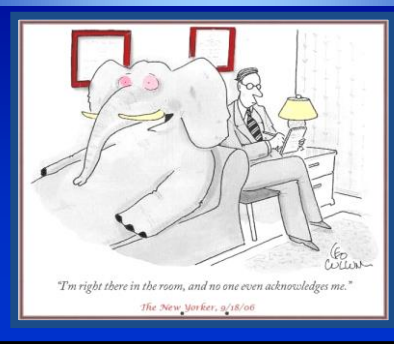
Pathological criteria for diagnosis of subacute and chronic hypersensitivity pneumonitis (surgical lung biopsy):

- Subacute hypersensitivity pneumonitis: cellular bronchiolitis or centrilobular scarring, plus interstitial lymphoplasmacytic infiltrate, and poorly formed non-necrotising granulomas.
- Consistent with chronic hypersensitivity pneumonitis: interstitial fibrosis with a pattern of non-specific interstitial pneumonia, organising pneumonia or usual interstitial pneumonia, and features atypical for usual interstitial pneumonia, including prominent peribronchiolar metaplasia, marked interstitial lymphoplasmacytic infiltrates, lymphoid aggregates without germinal centres, relatively prominent organising pneumonia, granulomas, and constrictive or obliterative bronchiolitis.[16] On the basis of the most recently published guidelines,[1] prominent centrilobular and bronchiolocentric lesions were judged atypical for idiopathic pulmonary fibrosis and favoured a diagnosis of chronic hypersensitivity pneumonitis.

Some reservations about diagnoses

- In 16/20 CHP cases, some support from biopsy
- However, much emphasis on immunological signal
- However, likely that CHP diagnoses had been missed in many cases

The elephant in the room: patients who do not fit into a classification



The problem of diagnostic overlap

- Diagnostic criteria do not capture all observed disease
- Many patients lie outside Categories
- Bywaters' Cheshire Cat syndrome: often we see the smile of the Cheshire cat but not the cat itself

Unclassifiable disease

- Sometimes incomplete data, sometimes overlap between entities, sometimes no clear first choice diagnosis
- Some have opposed a formal entity of unclassifiable disease as it allows clinicians to be lazy
- Does multidisciplinary diagnosis reduce the likelihood of unclassifiable disease?

ORIGINAL ARTICLE
INTERSTITIAL LUNG DISEASE

Prevalence and prognosis of unclassifiable interstitial lung disease

Christopher J. Ryerson[1], Thomas H. Urbania[2], Luca Richeldi[3], Joshua J. Mooney[4], Joyce S. Lee[4], Kirk D. Jones[5], Brett M. Elicker[2], Laura L. Koth[4], Talmadge E. King Jr[4], Paul J. Wolters[4] and Harold R. Collard[4]

Eur Respir J 2013; 42: 750–757 | DOI: 10.1183/09031936.00131912

Features of series

- Large retrospective series of 1370 patients
- Disease unclassifiable in 10% of cases
- Unclassifiable disease the fourth most prevalent entity
- *This series built with an ethos of routine diagnostic biopsy, pre MD diagnosis*

Biopsy viewed as diagnostic gold standard

- "To have a biopsy is to have a diagnosis"

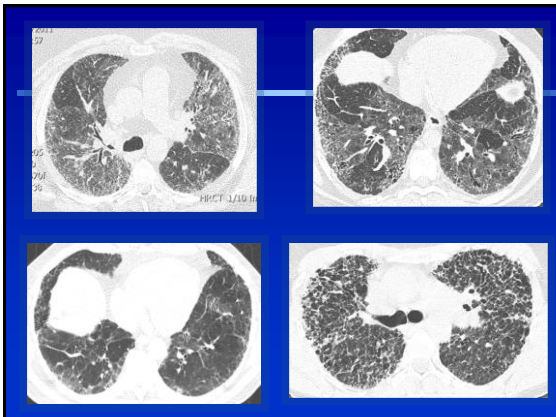
Reasons for unclassifiable ILD	
Too old or frail for lung biopsy	68
Conflicting clinical, radiological and pathological data	24
Mild or stable disease	12
Insufficient tissue on lung biopsy	11
Declined biopsy	10

Eur Respir J 2013; 42: 750–757 | DOI: 10.1183/09031936.00131912

- This presupposes that a) biopsy = truth data; and b) a biopsy can almost always be performed

How does multidisciplinary diagnosis help?

- The prevalence of unclassifiable disease rises whenever there is an articulate and out-spoken radiologist on site
- EJ Potchen once observed that "the only utility of a diagnostic test *(or guideline)* is to reduce confusion"
- Multidisciplinary diagnosis often increases confusion
- But it is a necessary confusion……



In all four cases …….

- Inexorable progression despite treatment
- IPF course, not acute lung injury
- Biopsy: classical UIP
- Subsequent inexorable progression to death

IPF with atypical HRCT appearances

In all four cases, strong clinical suspicion of IPF

In all four cases, biopsy undertaken with patient aware of the probable diagnosis

How is the diagnosis classified by ATS/ERS guidelines?

IPF: Multidisciplinary CT with Histopathological Input

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Raghu G, Collard HR, Egan JJ, et al. Am J Respir Crit Care Med 2011;183:788-824.

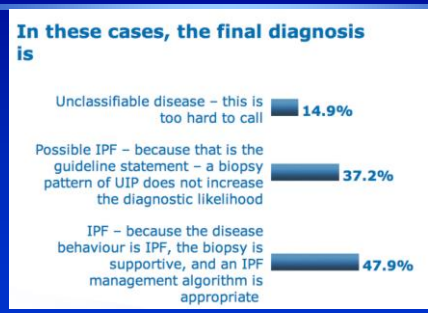
Question

In these cases, the final diagnosis is

Unclassifiable disease – this is too hard to call

Possible IPF – because that is the guideline statement – a biopsy pattern of UIP does not increase the diagnostic likelihood

IPF – because the disease behaviour is IPF, the biopsy is typical, and an IPF management algorithm is appropriate



Berlin IPF AIR meeting, November 2011

BMJ

BMJ 2014;348:g3725 doi: 10.1136/bmj.g3725 (Published 13 June 2014)

ANALYSIS

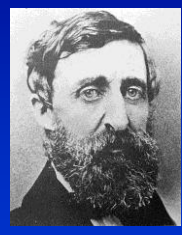
ESSAY

Evidence based medicine: a movement in crisis?

Trisha Greenhalgh and colleagues argue that, although evidence based medicine has had many benefits, it has also had some negative unintended consequences. They offer a preliminary agenda for the movement's renaissance, refocusing on providing useable evidence that can be combined with context and professional expertise so that individual patients get optimal treatment

Trisha Greenhalgh *dean for research impact*[1], Jeremy Howick *senior research fellow*[2], Neal Maskrey *professor of evidence informed decision making*[3], for the Evidence Based Medicine Renaissance Group

Henry David Thoreau (1817-1862)



Any fool can make a rule
And any fool will mind it

The question is not what you look at but what you see

{No-one of real intelligence believes something merely because some authority says that it is so}

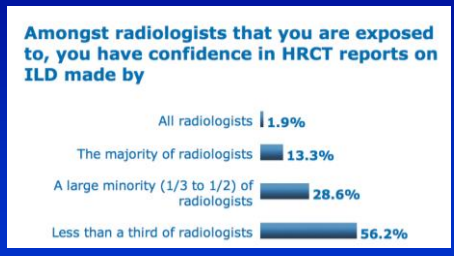
But let us consider the growing power of radiologists

HRCT appears to be a new gold standard – a diagnosis of IPF cannot be made if HRCT appearances are atypical

Amongst radiologists that you are exposed to, you have confidence in reports on the likelihood of IPF made be

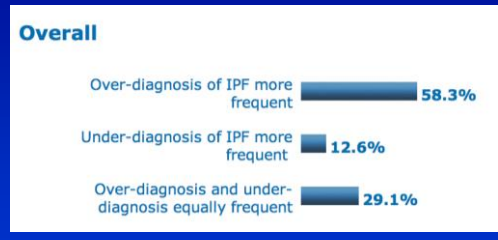
1. All radiologists
2. The majority of radiologists
3. A large minority (1/3-1/2) of radiologists
4. Less than a third of radiologists

Accuracy of radiological diagnoses….



Berlin IPF AIR meeting, November 2011

ATS/ERS guidelines – a tidal wave of HRCT misdiagnosis



Berlin IPF AIR meeting, November 2011

A tidal wave of HRCT misdiagnosis

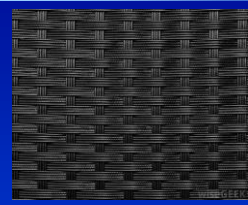
- Guideline recommendations that are complex and require reading of small print are, in reality, written for experts
- Experience has demonstrated that the majority of radiologists cannot apply the current HRCT diagnostic recommendations
- This is a MAJOR problem

True MD diagnosis is not governed by inflexible rules

- It consists simply of review of all relevant data in each individual patient
- No formula can be written for this process because the level of data varies so strikingly in each patient
- The process is one of logic and commonsense
- The true value of MD diagnosis is bringing together trained minds in order to reconcile and debate

The warp and the weft of multidisciplinary diagnosis

A metaphor for diagnostic practice



Warp = the bedrock (e.g. guidelines for diagnosis)

Weft = everything that is individual in patients and in multidisciplinary groups…… personality

Doctors are the most competitive people on this planet

- The opening stanzas in guideline groups…..
- The Professor of Consensus Agreement
- How can one combat this to achieve an outcome?
- How do multidisciplinary groups ever get started?`

In the end, banter is the key

Politeness is the poison of collaboration

Edwin Land

As always in a musical collaboration, one has to like each other – as simple as that

Klaus Schulze

Many ideas grow better when transplanted into another mind than in the one where they sprung up

Oliver Wendell Holmes

Minimal standards and desirable features: multidiscplinary groups

The musings of an ERS Task Force
IPF consensus statement

Frequency	Monthly	Weekly
Patient selection	Disease not fully characterised. Patients with classical features do not require review	Addition of some characterised patients in order to audit diagnostic practice and to educate meeting attendees. New/less experienced MD groups should review most patients.
Nature of meeting	Direct contact, face by face or via telelink, between clinician, radiologist and pathologist	Public forum with forensic discussion by participants and audience members, with full access to relevant imaging and pathology
Participants	Clinician, radiologist, pathologist with a declared interest in ILD. If not experienced, linkage to experienced group needed (e.g. electronic transmission of images, review of slides, telephone or e mail discussion of clinical aspects)	Two clinicians, radiologists and pathologists (to cover absences). Multidisciplinary co-ordinator, rheumatologist.
Goals of meeting	Diagnosis Review of diagnostic possibilities prior to biopsy	Diagnosis Review of diagnostic possibilities prior to biopsy Discussion of treatment in highly selected patients Review of evidence of disease progression during follow-up in selected patients

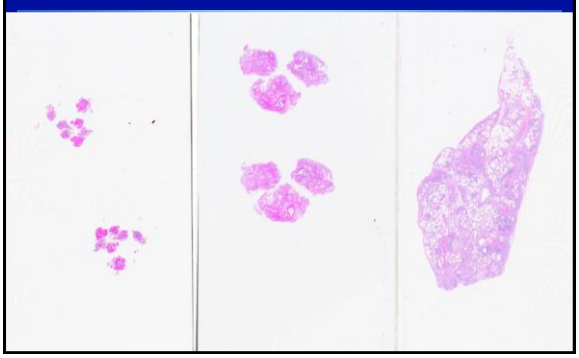
MDD: a potent research tool

Cryobiopsy: background

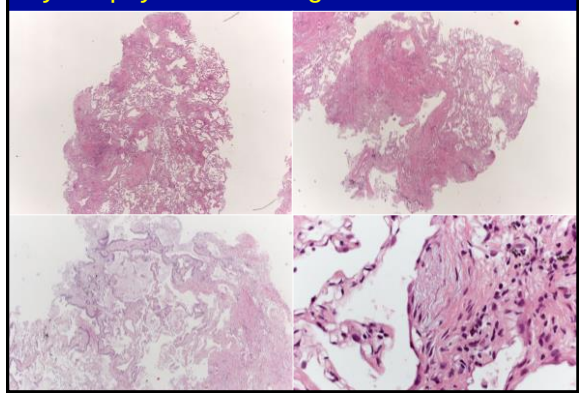
- Transbronchial biopsy: inadequate in IIPs - strong -ve recommendation in 2011 IPF guideline
- With a freezing technique, able to achieve much larger biopsies (technique of Juergen Hertzel)
- Four to six biopsies routinely taken

My thanks to Venerino Poletti for the slides that follow

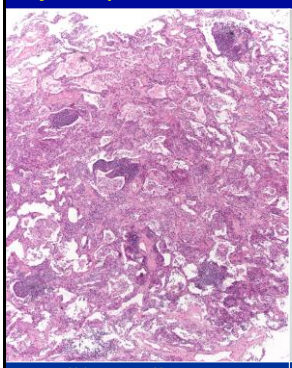
TBB Cryobiopsy VATS



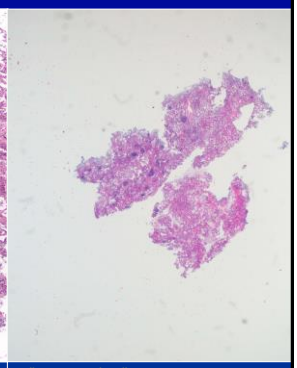
Cryobiopsy: UIP with high confidence



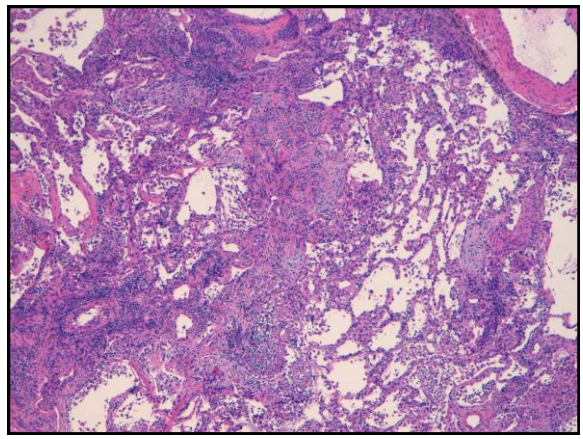
Cryobiopsies inconsistent with IPF



Hypersensitivity pneumonitis



Collagen vascular disease



Prospective study of transbronchial lung cryobiopsy

- 69 cases
- Three pathologists (Cavazza A, Colby TV, Rossi A)
- Pathologists highly confident that material sufficient to define pattern in 52 of 68 cases (76%), including 36 patients with a pattern of UIP
- Excellent agreement between pathologists on the presence of a UIP pattern (kappa = 0.83)
- TBLC in the diagnosis of fibrotic ILD appears safe and feasible and may offer an alternative to SLB – this requires further studies

Casoni GL et al. PLoS One 2014; e86716.

Issues

- Mortality - in three series and >400 patients, <1%
- Pneumothoraces in over 20% - but beleeding rare with central biopsies
- Prognostic value yet to be quantified

The advent of cryobiopsy in Forlì: «sneaking technology»

	2008		2009		2010		2011		2012		2013		Total	
New IPF diagnoses	36		27		26		55		40		52		236	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	*Age: median (Range)Y*
CRYO	0	0%	0	0%	0	0%	22	40%	18	45%	24	46%	64	62 (33-78)
SLB	15	42%	8	30%	7	27%	3	5%	3	8%	7	13%	43	57 (42-74)
Cases with cryoTBB+SLB	0		0		0		0		2		4		6	

Biopsy confirmed IPF

SLB 42% in 2008
13% in 2013

The diagnostic accuracy of bronchoscopic lung cryobiopsy in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis.

Sara Tomassetti[1], Athol U Wells[2], Ulrich Costabel[3], Alberto Cavazza [4], Thomas V Colby [5], Giulio Rossi [6], Nicola Sverzellati [7], Angelo Carloni [8], Elisa Carretta [9], Matteo Buccioli [1], Paola Tantalocco [1], Gian Luca Casoni[1], Claudia Ravaglia[1], Christian Gurioli[1], Alessandra Dubini [10], Sara Piciucchi [11], Jay H Ryu [12], Venerino Poletti[1].

TABLE 1. Clinical and radiologic characteristics of the two groups of patients undergoing bronchosopic lung cryobiopsy (BLC) or surgical lung biopsy (SLB).

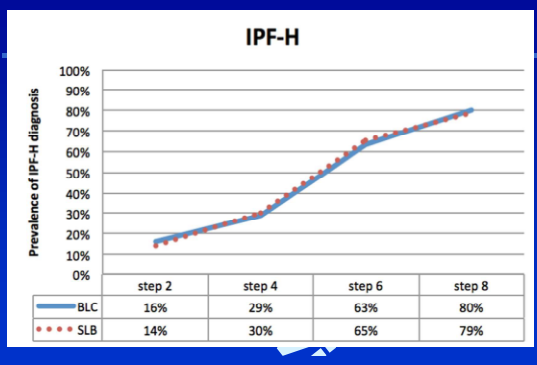
	BLC	SLB	p-value
Cases, N (%)	58 (50)	59 (50)	
Age, median (range)	59 (29-77)	59 (34-74)	0.893
Males, N (%)	27 (47)	28 (47)	0.756
Cigarette Smoking, current/former/never, N (%)	1/25/32 (2/43/55)	4/25/30 (7/42/51)	0.271
FVC, % , median (range)	82 (50-123)	81 (27-133)	0.514
TLC, %, median (range)	75 (46-105)	76 (26-123)	0.763
DLco, %, median (range)	55 (29-76)	55 (29-106)	0.823
O2 use, N (%)	1 (2)	3 (6)	0.59

Abbreviations: FVC, forced vital capacity; TLC , total lung capacity; DLco, carbon-monoxide diffusion coefficient; O2 use, supplemental oxygen use at rest (any flow rate).

Methodology

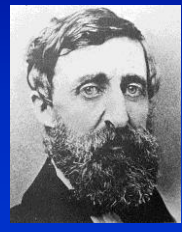
- Step 1: Diagnosis by individual specialist
- Step 2: Consensus of clinicians/radiologists
- Step 3: Add BAL: diagnosis by individual specialists
- Step 4: Consensus of all
- Step 5: Add histology
- Step 6: Consensus of all

- Step 7 & 8: Follow-up data



Henry David Thoreau (1817-1862)

In summary



Any fool can make a rule
And any fool will mind it

The question is not what you look at but what you see

{No-one of real intelligence believes something merely because some authority says that it is so}