Why All This?
The history of clinical research design from the human medical side of the fence

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What can Vet Med learn from clinical research design evolution in Human Medicine?
• Pitfalls?
• Shortcuts?
The Result: Evidence-based Medicine (EBM)

What is "Evidence-based Medicine"?
EBM is "an approach to practice in which the clinician is aware of the evidence in support of their clinical practice and of the strength of that evidence" (1992, McMaster U, Hamilton, Ontario)

Practicing EBM is simply practicing knowing the answers to two questions:
1. What is the evidence for that?
   • "that" being the use of a diagnostic test, establishing a prognosis, administering a therapy, or recommending a preventive measure
2. How good (strong) is this evidence?
   • How likely are the conclusions based on the evidence correct?

This implies awareness of the kinds of evidence and possession of the skills to critically assess evidence

Most discussions are about how to do it. My purpose is to provide background on why it developed

EBM resulted from the coalescing of Threads:

- Historical "Tree Shakers"
- New McMaster PBL Medical Curriculum
- Teaching of Literature Evaluation
- Emergence of Clinical Epidemiology
- Evolving Computer Technology

1992 term "Evidence-based Medicine" first used
15 Yrs
15,738 Medline hits
~3,000 / year for last 5 years

Note: EBM processes are still evolving!

Some quick definitions:
Belief:
• State of mind after accepting a concept or idea, becoming part of further related thinking
  • Internalized deeply, belief becomes unconscious intuition
  • The expert (drives students nuts)
• Belief occurs:
  • after deliberate, systematic, critical thinking
  • with immediate, non-reasoned, uncritical acceptance
  • Your choice
• If in error, accepting a more correct belief later is more difficult than if no previous belief were held

Learning Cycle

Nature of Human Thinking

"Human nature" is to:
- Weigh information consistent with current belief heavier
- Ignore or discount discordant information
- Typically search for additional belief-confirming data rather than belief-refuting data
- **EX:** Selective necropsy to confirm a gross diagnosis (drives pathologists nuts)
- Prior belief biases observation because it subtly changes perception, particularly of vague or ambiguous characteristics
- **EX:** Radiographs, clinical signs
- This bias occurs unconsciously and despite the observer’s best intentions!

The fundamental reason for "blinding"!

Evidence-based Belief

**Rational Belief:**
- A belief that satisfies suitable standards of evidential support

**Evidence:**
- That which tends to show that something is the case or is used to prove or support something

Implicit in this definition is that evidence varies in strength


Anecdotal Evidence

- The occurrence of desired event(s), such as medical recoveries
  - **Case reports**
- Often interpreted as due to the therapy applied and thus validating the theory on which the therapy was based
- Problems:
  - The probability of apparently unusual events is considerably higher than expected by intuition (birthday paradox – 30% – 70%)
  - Unrecognized factors (confounders) may have invalidated the initial prediction
  - Because anecdotes are extremely weak evidence, accumulating similar anecdotes does not significantly increase support of a theory – **Case series**

The plural of anecdote is not evidence!

Analogical Evidence

- Reasoning from comparing known similarities between two systems in which a relationship known to exist in one but not the other is reasoned to exist in the other as well
  - **If drug X has been shown to be effective against disease Y in a species Z, reasoning that the same relationship exists between similar drugs, similar diseases or similar species**
  - Susceptible to error because of the likelihood that different but unknown factors are operating in the two systems
  - Very common reasoning in veterinary medicine
  - Necessary basis for action when empirical evidence is lacking
  - Minor species
  - Disease mechanisms are often established in selected species (rodents) and then extrapolated to other species in which direct investigation is impractical

Empirical Evidence (Facts)

- Knowledge obtained by looking rather than reasoning or feeling
  - **Empirical:** based on verifiable observation or experiment, not on theory or pure logic (data)
  - Objective findings (not their interpretation!) derived from formal observational or experimental procedures that are repeatable (verifiable) and that meet currently accepted standards of design, execution, and analysis
  - Strengthened by rigorous observation or conducting experiments designed to have a clear, unequivocal supporting or refuting outcome
  - Weakened by the degree of opportunity for other explanations that could account for the findings
    - Your judgment as to the impact of this opportunity

Every little kid is an empiricist: "Don't touch the stove; it's hot!"

Considering Empirical Evidence

- As the opportunity for verification (repeatability) and for assessment of strength is key, the methods used to acquire the evidence must be described or referenced sufficiently to enable this verification and assessment (transparency)
  - **Remember:** The empirical evidence can be correct (e.g., the sun "rises" predictably) but the underlying theory that it is believed to support is wrong (e.g., the sun orbits around the earth)

The importance of the "materials and methods" fine print
Dogma:
• Those beliefs put forth without supporting empirical evidence with which to judge strength
  • Not presented for efficiency (textbooks, notes)
  OR
  • Unevaluated hypotheses or uncrirical observation without awareness of the effects of chance, biological variation and observer bias (authoritative or established opinion)
• Repetition across sources or people, whatever their qualifications, does not change the status of such information (textbooks?)
• Some dogma is right, some dogma is wrong; the problem is which is what?

Recognize:
• Most of the veterinary curriculum is taught as dogma (little time to do otherwise)
• Information necessary to judge its strength is not provided (imagine the length of notes and textbooks if it was!)
• Habits of deliberate, systematic, critical evaluation are not well developed
• Uncertainty is hidden (imagine student frustration if it was not)
• Analogical evidence is the basis of reasoning taught in much of the curriculum
• Most individual case experience is anecdotal
  • Recall the “3/n rule”

Literature Classification vs. Type of Publication

- The distinction is important!

EBM Story Timeline & Dignitaries

- Early 1900’s - Ernest Codman’s (1869 – 1940) “The End Result Idea” led to empirical outcome evaluation

- “Tree Shakers”:
  • Florence Nightingale
  • Ignaz Semmelweis
  • Joseph Lister
  • John Snow
  • William Harvey
  • William Osler

Ernest Codman, 1869-1940: A Pioneer of Evidence-Based Medicine: The End Result Idea

- “The End Result Idea: The common sense notion that every hospital should follow every patient it treats, long enough to determine whether or not the treatment has been successful, and then to inquire ‘if not, why not?’ with a view of preventing similar failures in the future.”
- End Result System of Hospital Organization: Tracking and publishing the results of hospitals and of individual surgeons
- Result: Harvard fired him as surgery instructor
- Led to establishing the American College of Surgeons

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- Late 1940’s – Professor Austin Bradford Hill’s (1897 – 1991) use of blinded randomization in a controlled trial of streptomycin for human tuberculosis established the RBCT as the evidence “gold standard”
Use of randomisation in the Medical Research Council’s clinical trial of streptomycin in pulmonary tuberculosis in the 1940s


- Demand for Streptomycin, isolated in 1943, far exceeded supply
- Spontaneous cures of the respiratory form occurred, confounding studies
- Prior poorly controlled studies led to the adoption of inefficacious, even harmful, treatments
- Blind randomisation relieved the MRC’s clinicians of responsibility for deciding who would be treated
- Trial design was an integration of prior developments rather than novel

Even giants stand on giant’s shoulders

- AB Hill “quite simply the world’s leading medical statistician”
- Physician smoking study with Doll

**Tables from the original paper**


| Streptomycin cost | $320,000 |

**Table 2: Outcomes of tuberculous appearance or death in identical groups**

<table>
<thead>
<tr>
<th>Radiological appearance</th>
<th>Streptomycin Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate improvement</td>
<td>14 (53%)</td>
<td>17 (60%)</td>
</tr>
<tr>
<td>No improvement</td>
<td>17 (60%)</td>
<td>15 (55%)</td>
</tr>
<tr>
<td>Moderate or slight improvement</td>
<td>5 (25%)</td>
<td>12 (44%)</td>
</tr>
<tr>
<td>Convalescence</td>
<td>4 (21%)</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>Death</td>
<td>4 (21%)</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>Total</td>
<td>55 (100%)</td>
<td>55 (100%)</td>
</tr>
</tbody>
</table>

**The name behind the Cochrane Collaboration**

[http://www.cochrane.org/](http://www.cochrane.org/)

Archie Cochrane


- In 1976, Dr. Kerr White, Rockefeller Foundation deputy director for health services, was giving a talk on evidence-based medicine
  - He was telling his audience that only 15% to 20% of doctors’ interventions had been proven to do more good than harm, when a voice yelled out in mid-sentence: “Kerr, you’re a damned liar. You know perfectly well that it isn’t more than 10 percent!”
  - The voice belonged to Dr. Archie Cochrane — British epidemiologist, evidence-based medicine pioneer, and a man never afraid to speak his mind

**Was it really 10%? What is the evidence? Does it matter?**

**What proportion of Medicine is evidence-based?**

[http://www.shef.ac.uk/scharr/ir/percent.html](http://www.shef.ac.uk/scharr/ir/percent.html)

**Resource Guide (Andrew Booth):**

- 18 studies, executed between 1995 and 2000, to determine the strength of evidence supporting clinical procedures
- Of ~128 procedures per study (range of 40 to 1,990 procedures)
- 38% were supported by RBCT Type I (strongest) evidence
- 22% were not supported by convincing experimental or non-experimental evidence!

**EBM Story Timeline & Dignitaries**

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- Late 1940’s – Professor Austin Bradford Hill’s (1897 – 1991) use of blinded randomization in a controlled trial of streptomycin in human tuberculosis established the RBCT as the evidence “gold standard”
- 1972 – Dr. Archie Cochrane’s (1909 – 1988) bestselling book *Effectiveness and Efficiency: Random reflections on health services*
  - Challenged physicians to base the selection of procedures and interventions on the RBCT

**Is examining dogma important?**

**What proportion of veterinary medicine is dogma?**
Evidence of Process Problems
Pseudodoxia pediatrica
NEJM 232:691-697 (1945)

Three groups of pediatricians examined children suffering from tonsillitis:

- **Classic Tonsillectomy Study**
  - 389 11 year old children with tonsillitis
  - 174 (45%) Tonsillectomy Recommend
  - 214 (55%) Tonsillectomy Not Recommend

- **Is checking for dogma important?**
  - 389 11 year old children with tonsillitis
  - Examined by physicians
  - 214 (55%) Tonsillectomy Not Recommend
  - 174 (45%) Tonsillectomy Recommend

  - **Sneaky Epidemiologists**
    - (Blind to previous exam results)
    - Examined by other MD’s
    - 99 (46%) Tonsillectomy Recommend
    - 214 (55%) Tonsillectomy Not Recommend

  - **What do you think the other MD’s recommended?**
    - SX

  - **Epidemiologists couldn’t believe results**

  - **What do you think the next MD’s recommended?**
    - SX

  - **Coin Flip!**
    - 115 (54%) Tonsillectomy Not Recommend
    - 64 (56%) Tonsillectomy Recommend

  - **What like this is happening in animal health?**
    - If we haven’t looked “well”, we don’t know!

Clinician-Discoverers – Marshall, Warren, and H. pylori
NEJM 353(23):2421-2423

The Nobel Prize in Medicine 2005
"for their discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease"

Fascinating story of:
* How they challenged the dogmas that:
  - Due to acid, the stomach was sterile
  - Stress and spices cause ulcers
  - Serendipity
  - How advancing technology enabled their research
* How the medical community resisted their findings

Challenging Dogma might win you a Nobel Prize

Evidence of Process Problems

Similar to the earlier Tonsillectomy study:
* In Vermont, the chance of having one’s tonsils removed were 8% in one community and 70% in another
* Surgeons given written descriptions of surgical problems split down the middle ... half recommending surgery, half not
* When surveyed again two years later, the same surgeons often disagreed with their previous opinions, with 40% changing their recommendations
* Variability occurs because physicians must make decisions about phenomenally complex problems, under difficult circumstances, with little support
* Physicians are in the impossible position of not knowing outcomes of different actions, but having to act anyway
Evidence of Process Problems

- Cardiologists evaluating high quality angiograms for stenosis of coronary vessels:
  - ... asked to estimate whether the percentage of stenosis ... was greater or less than 50%, they disagreed on 60% of the patients
  - ... on two successive readings of the same angiograms, the observers changed their minds from 8% to 37% of the time, depending on the vessel segment
- In general, observers looking at the same thing will disagree with each other or even with themselves from 10% to 50% of the time
- Pathologists reading human biopsy slides (Not just a clinician's problem)
  A panel of expert pathologists disagreed two or more times on the interpretation of 38% of human skin melanoma biopsy specimens as benign or malignant. (Hum Pathol 27:528-31 (1996))

Autopsy evidence of Physician Diagnostic Error Rates
Changes in rates of autopsy-detected diagnostic errors over time:

- 53 autopsy series published 1966 - 2002
- 24% major error rate (4.1% - 49.3%)
  - Involved 1st cause of death but did not affect outcome
  - 9% class I error rate (0% - 20.7%)
  - Likely resulted in death!
- Accounting for steady improvements, current major error rate is likely 8% - 24% and class I rate is likely 4% - 7%
- Of 850,00 individuals dying in US hospitals each year, without misdiagnoses 34,850 would have survived to discharge

Problems with Evaluation of New Interventions
Statistics and Ethics in Surgery and Anesthesia
Science 198:684-689 (1977)

How often do new therapies turn out to be superior when they are tested and how much better or worse are they likely to be?
- MEDLARS search for papers published 1964 - 1973
- Found 46 papers that satisfied four criteria:
  1. Randomized trial
  2. At least ten people in each group
  3. Compare surgical or anesthetic treatments
  4. Written in English (investigator's limitations)
- Found 11 papers that were non-randomized but met rest of criteria

Non-randomized comparison results

<table>
<thead>
<tr>
<th>Preference</th>
<th>Primary</th>
<th>Secondary</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I &gt; 5</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>I = 5</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>I = 5 (dispointed)</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>S &gt; 1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>8</td>
<td>11</td>
</tr>
</tbody>
</table>

“By and large, the distribution leans more favorably toward innovations than that seen in Table 1”

“A tendency for nonrandomized trials to favor innovations is frequently noted”

Randomized comparison results

<table>
<thead>
<tr>
<th>Preference</th>
<th>Primary</th>
<th>Secondary</th>
<th>Total</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>I &gt; S</td>
<td>1</td>
<td>5</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>I = S</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>I &lt; S</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>I = S (different)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>S &gt; S</td>
<td>6</td>
<td>5</td>
<td>11</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>28</td>
<td>47</td>
<td>(99)</td>
</tr>
</tbody>
</table>

Table 1. Qualitative comparisons between innovations (1) and standards (3) stratified by primary and secondary therapies. Where a paper had two comparisons, each was weighted one-half.

Gastric freezing for ulcers, . . .
Human medicine is littered with these!

Degree of control vs. Investigator Enthusiasm

<table>
<thead>
<tr>
<th>Degree of control</th>
<th>Degree of enthusiasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-controlled</td>
<td>Marked</td>
</tr>
<tr>
<td>Poorly controlled</td>
<td>Moderate</td>
</tr>
<tr>
<td>Uncontrolled</td>
<td>None</td>
</tr>
</tbody>
</table>

- Muench has a set of statistical laws, one of which says "nothing improves the performance of an innovation as much as the lack of controls"
- Because tables for other therapies have similar results, one must be cautious in accepting results of weakly controlled investigations
- The rows for "poorly controlled" and "uncontrolled" studies suggest that repeated, weakly controlled trials are likely to agree and build up an illusion of strong evidence because of the large count of favorable studies

Concurrent comparisons!
Do Study Design Weaknesses Matter?

Meta-analysis of empirical studies relating key methodological quality aspects of controlled trials to their effect estimates

- Size of squares is proportional to inverse of variance of estimate
- Odds Ratios from trials with inadequate blinding were 30% more "beneficial" than those with adequate blinding

You betcha!

A comparison of results of meta-analysis or randomized control trials and recommendations of clinical experts: Treatments for Myocardial Infarction


• Contrast the results from 182 RCTs with the recommendations of 43 review articles and 100 textbook chapters by publication date
• Classified recommendations of experts as:
  1. Routine – therapy should be used routinely unless there is a specific but uncommon contraindication
  2. Specific – therapy should be used only in selected patients with a particular indication
  3. Rare/Never
  4. Experimental
  5. Not mentioned

This study took a huge amount of work! And it had big impact – 606 citations to date

Problems with Information Synthesis & Dissemination

A comparison of results of meta-analysis or randomized control trials and recommendations of clinical experts: Treatments for Myocardial Infarction


- Evolved the patient presentation to the appropriateness of a treatment

- Used a standard format to present results of a treatment

Continuing to recommend a questionable therapy on basis of biological plausibility

- Narrative reviews > Systematic Reviews

The Medical Review Article: State of the Science


- Evaluated 50 reviews published 6/85 to 6/86 in Ann Intern Med, Arch Intern Med, JAMA, NEJM using 8 criteria from guidelines for information syntheses
  - 34% met 3 of 8 criteria
  - 64% met 4 or 5 criteria
  - 2% met 6 of 8 criteria
  - 6% used quantitative synthesis
  - 42% mentioned future research directions
- These results indicate that current medical reviews do not routinely use scientific methods to identify, assess, and synthesize information
- Medical reviews are often subjective, scientifically unsound and inefficient
- The methods used in this systematic assessment of reviews are proposed to improve the quality of future review articles

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The Problems of External Validity!
The Medical Review Article Revisited: Has the Science Improved?

Evaluated all the reviews on clinical topics published in 1996 in:
• 3 of 4 randomly selected core high impact journals (Ann Intern Med, JAMA, NEJM)
• 3 of 8 randomly selected core journals with lower impact factors
• 5 blinded raters used 10 validated criteria

1987: 64% met 4 or 5 of 8 criteria!

Progress in the wrong direction?

Systematic Reviews: Synthesis of the best evidence for clinical decisions

Steps in traditional narrative review
• Write what we think is important
• Find references to support our view
• Insert these as needed

Steps in systematic review
• Question formulation
• Exhaustive literature search
• Relevance screening
• Quality assessment
• Data extraction and synthesis
• Written report
• Dissemination
• Repeat process to update

Reviews “outsource” responsibility for critical evaluation

On-line Systematic Review Systems
The Current Path of Human Medicine

• Developed because:
  ▪ No clinician can read all of the relevant literature
  ▪ Even expert searchers find only half of the RBCTs in MEDLINE
  ▪ Systematic reviews often quickly outdate
  ▪ Busy clinicians do not have the time to practice EBM on a paper-by-paper basis! (Know how to do it? – Yes!)
  ▪ On-line collaborations enable experts at remote sites to cooperate in establishing and updating systematic reviews addressing important clinical questions

Time is the busy clinician’s scarcest resource
Usefulness = (Relevance X Strength) / Work
Initial EBM approaches overlooked this fact!

The Cochrane Collaboration
"The reliable source of evidence in health care"
http://www.cochrane.org/

• International non-profit dedicated to making current, accurate information available worldwide
• Produces systematic reviews, promotes search for sound evidence and develops tools for performing reviews
• The Cochrane Database of Systematic Reviews is published quarterly
http://www.thecochranelibrary.com
• Volunteers work in a Cochrane Review Group with an editorial team to prepare and maintain the reviews, applying the Cochrane Review quality standards
• Activities of the Collaboration are directed by an elected Steering Group and are supported by staff in Cochrane Entities (Centres, Review Groups, Methods Groups, Fields/Networks) around the world

Cochrane Reviewers’ Handbook (250+ pages on-line)
http://www.cochrane.dk/cochranehandbook/htbook.html

The Science of Information Synthesis

Per Jan Sargeant, McMaster Univ
2nd Symposium on EBVM, MSU (2006)
Knowledge for Knowledge Translation: The Role of the Cochrane Collaboration

- 50 Review Groups
- 10 Methods Groups
- 12 Centres
- 13,000 volunteers

Major undertaking in human medicine

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- 1972 – Dr. Archie Cochrane’s (1909 – 1988) bestselling book "Effectiveness and Efficiency: Random reflections on health services" challenged physicians to base the selection of their on the RBCT.
- Late 70’s to present – Evidence of problems began accumulating from studies undertaken after Archie Cochrane’s challenge
- 1992 – The paradigm of EBM began coalescing from several pathways to begin addressing these problems
  - Journal clubs, critical review checklists, . . . . . > EBM

Impediments due to Human Nature


- There is confusion and misunderstanding about the concepts of knowledge translation, knowledge transfer, knowledge exchange, research utilization, implementation, diffusion, and dissemination
- The implications of knowledge translation for continuing education in the health professions include the need to base continuing education on the best available knowledge, the use of educational and other transfer strategies that are known to be effective, and the value of learning about planned action theories to be better able to understand and influence change in practice settings
- Despite the considerable resources devoted to health sciences research, a consistent finding from the literature is that the transfer of research findings into practice is often a slow and haphazard process

Gordon Guyatt (one of the original EBM Gurus)
Respir Care 46(11):1201-1211 (2001)

- A cardiologist coming back from a recent meeting told me that there was a recent trial that showed that the IIb/IIIa inhibitors probably did not reduce adverse outcomes in people who were presenting with acute ischemic syndromes
- And all the cardiologists got up and said "Wait till the publication's out; we have to look very carefully at that. There may be something wrong with that trial"
- By nature, our brains are refractory to new ideas

- On the other hand, a recent report of a single big trial suggested that clopidogrel reduces adverse outcome events in people who were presenting with acute ischemic syndromes, given in addition to aspirin
- Everybody walked out saying, "Yes, let's do it."
- People have entrenched biases, beliefs, and ways of doing things. We tend to be resistant to new evidence, and we're more receptive to some new things than others
- If evidence contradicts our general mindset, we're much more resistant

Gordon Guyatt
Respir Care 46(11):1201-1211 (2001)

- So when you’re talking about changing behavior, evidence is one relatively small factor in changing anybody’s behavior, be it clinicians or other people
- We have to look at other strategies for changing people’s minds and, once we’ve changed their minds, other strategies for changing their behavior
- So there’s the rational part of it that we want to get right, and there is also the changing behavior part that we need to get right

Human behavior is hard to change!
What Is Evidence-Based Medicine and Why Should It Be Practiced? (Respir Care 46(11):1201-1211 (2001))

- Responding to the limitations of traditional expert recommendations as a guide to clinical practice, EBM is a paradigm shift in the way clinicians learn and practice medicine.
- Practicing EBM requires careful examination of evidence, using explicit formal rules, followed by judicious application to clinical decision-making.
- We believe that this approach leads to optimal patient care.
- EBM facilitates an explicit decision-making process that is transparent and thus open to evaluation and improvement.

Society likely will expect this of veterinarians.

I may well be sawing the limb off but:
Based on the evidence from human medicine, the consequences of not going down the EBVM path are huge!

What can we learn from human medicine?
- Where were they when they started?
- How are they getting from there to EBM?
- What problems did the pioneers encounter?
- What problems are they encountering now?
- How are they similar / dissimilar from us?

What should we be learning from human medicine?
- Veterinary evidence exists for every human medicine problem I've shown you.

George Santayana
(poet, philosopher, essayist 1863-1952)

Saying as commonly attributed:
- Those who cannot learn from history are doomed to repeat it

What he actually said:
- Those who cannot remember the past are condemned to repeat it
  From Reason in Common Sense, vol. 1 of The Life of Reason

Broader Issues:
Consilience across academic disciplines:
- Do we know & account for our intrinsic mental limitations?
- How do adults (students or practitioners) learn best?
- What motivates or blocks learning? Adoption?
- Basic sciences vs. clinical contexts
- Students dealing with uncertainty
- Clinicians with out-dated paradigms

What knowledge foundation is required:
- To facilitate clinical decision making?
- To facilitate adoption of new paradigms?

Information Science:
- How do we best increase the value of our professional knowledge base?

EBVM is Personal Protection in the World of Ideas

Why "personal protection"?
Because of the way our minds naturally work if we let them!
- Be very careful what you put in that head, because you will never, ever get it out.  Cardinal Wolsey (1475-1530)
- It ain't so much the things we don't know that get us into trouble. It's the things we know that just ain't so.  "Artemus Ward" (Charles Farrar Browne, 1834-1887)
- It is impossible for anyone to learn that which he thinks he already knows.  Plutarch

As one wag observed, is the only route to change the dying of the "old guard"?
Fundamental Science Literacy

To understand EBVM, would the profession benefit from a sounder understanding of the fundamentals of science?

- **Philosophy of Science** - Wikipedia
- **History of Science** - Wikipedia

Why the fundamental processes of science and the scientific method were developed and why they are practiced:
- Why blinding, randomization and concurrent controls are essential
- The potential costs of compromises (case-control, cohort studies)

The Logic of Scientific Discovery:
- Hypotheses vs. theories vs. truth
- Proof or truth vs. uncertainty
- The anvil of independent replication

Although we all take science courses and have degrees with “science” in the title, most don’t understand science!

Consider our Learning:

- **Most of the veterinary curriculum is taught as dogma**
  - The information necessary to judge its credibility is not provided
  - Lectures, core textbooks
  - Habits of continual deliberate, systematic, critical thinking are not well developed (and, given resource limitations, possibly cannot be)
  - Analogical evidence is the most prevalent basis of reasoning taught in much of the curriculum
  - Most of everyone’s individual case experience remains anecdotal

Major Problem: Lack of Quality Evidence


- **OBJECTIVE**: Evaluate the literature reporting surgical interventions for canine cranial cruciate ligament (CCL) injury using EBVM
- **STUDY DESIGN**: Systematic literature review
- **METHODS**: Search through Medline, PubMed, VIN, and CAB Abstracts performed August 2004 identified 246 sources of information
- **Studies were evaluated for study design (retrospective, prospective, randomization), surgical technique, short- and long-term follow-up, and evidence classification**

Why did they pick this procedure? 

Evidence Strength Classification

- **Class I**: Systematic reviews based on multiple RBCT’s
- **Class II**: High quality clinical trials using historical controls, sound observational studies
- **Class III**: Uncontrolled case series
- **Class IV**: Expert opinion or extrapolated from other studies

This pyramid is important!

Evidence Strength Results

- **Class I**: 0 systematic reviews based on multiple RBCT’s
- **Class II**: 0 high quality clinical trials using historical controls, sound observational studies
- **Class III**: 5 uncontrolled case series
- **Class IV**: 23 expert opinion or extrapolated from other studies

Poor evidence has a price, particularly when its poor quality is not recognized!

The human literature is sufficiently deep that they seldom use studies less than class II.
Sir William Arbuthnot Lane
Scottish surgeon, 1856 - 1943

- Known for developing internal fixation to improve fracture alignment
- Started using silver wire, then screws followed by plates and screws
- Hence, the label "Lane’s plates"

Sir William Arbuthnot Lane

- Eccentric, regarded humans as machines
- Performed many total colectomies as a cure for "auto-intoxication"
- 10% mortality risk

The danger of authorities without supporting evidence

- CONCLUSIONS: At this time, the application of EBM suggests that there is not a single surgical procedure that has enough data to recommend that it can consistently return dogs to normal function
- CLINICAL RELEVANCE: An EBM paradigm did not provide sufficient evidence favoring 1 surgical technique for management of canine CCL injury


- CONCLUSIONS: At this time, the application of EBM suggests that there is not a single surgical procedure that has enough data to recommend that it can consistently return dogs to normal function
- CLINICAL RELEVANCE: An EBM paradigm did not provide sufficient evidence favoring 1 surgical technique for management of canine CCL injury


- Searched Pubmed and selected journals between 1994 and 2004 for analgesia papers that reported:
  - 'no difference' between experimental groups in the abstract, results or conclusion
  - Were randomized, prospective and blinded
- Found 46 studies of which 22 provided sufficient data for power analysis
- Performed power analyses to determine sample size for detection of 20%, 50% and 80% treatment effect with power of 80%
  - 5 (23%) had sufficient power to detect a 20% treatment effect
  - 12 (54%) had sufficient power to detect a 50% treatment effect
  - 18 (82%) had sufficient power to detect an 80% treatment effect

From some 800+ reports identified:
- "We are impressed with the small number of useful reports. . . while there are hundreds of reports in the literature, most suffer from one or more design flaws or limitations. . . it suggests that we may be making less than optimal recommendations on vaccine use because of a lack of clinically relevant information."
- "It is time to critically evaluate vaccination as a management tool"


- During a period in which 60 studies relevant to a particular veterinary clinical question were published in the veterinary literature, 5,400 studies were published in the human literature for the equivalent human clinical question
  - Almost a 100 to 1 ratio
- Many of these were based on inherently stronger study designs


- Limited evidence in the literature almost a decade later that this challenge was taken up
  - What is the long term impact of these open questions on producer usage of veterinarians?

Limited evidence in the literature almost a decade later that this challenge was taken up

- The most significant contribution of veterinary systematic reviews for some time to come will be identifying critical clinical research needs
  (Also noted by Cockcroft and Holmes)
Dangerous pitfalls for EBVM
Entrenchment and resistance of clinicians
• EBM is arguably the most important contemporary initiative committed to reshaping biomedical reason and practice
  • The move to establish scientific research as a fundamental ground of medical decision making has met with an enthusiastic reception within academic medicine, but has also generated considerable controversy
  • Cognitive dissonance from the pressure on clinicians to do something in the face of weak or non-existent evidence?

We are too small of a profession for EBVM to succeed in the face of clinician resistance

Dangerous pitfalls for EBVM
Not continually making clear the weakness of evidence in each EBM product
• Medical practices, clinical practice guidelines, . . . are claimed to be "evidence based" with increasing frequency
  • When is evidence sufficient for "evidence-based" to rightfully apply?
• "Friends" include practitioners of a crude version of EBM (uncritical acceptance of randomized controlled trials while rejecting all other forms of evidence)

Simply labeling something "EBVM" or a "systematic review" does not make it either. Yet it is human nature to do so!

Dangerous pitfalls for EBVM
The myth that veterinary academics alone will create EBVM
The number of human oncologists at a typical university cancer center equals all the boarded veterinary oncologists (Keene)
More physicians have privileges at the University of Washington Hospital than there are veterinarians in the entire state of Washington
The total 2005 NIH research budget was 28 billion $$; the total 2005 USDA research budget was 2 billion $$ and ½ of that was for plants

Data ownership issues
• Large entities may recognize a proprietary advantage in their data
• Large livestock units, large corporate practices
• Sources of compensation for data collection?
• Difficulties of collaboration and authorship across academic systems

Simply not enough academic clinician person-hours or $$$$

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Emerging Internet Technology
Internet is evolving rapidly in ways that facilitate community input and discussion
• How can these be used to facilitate EBVM?
Examples:
  • Blogs ("web logs") for maintaining collaboration
  • Wiki software for joint authoring
  • Zotero for sharing references
  • Social networking software for multicenter collaboration

Personal computers and the Internet
The core of the opportunity
• Take full advantage of this technology to facilitate multi-practitioner, multi-center collaboration
• Enables:
  • More rapid case accumulation
  • Broader base for external validity
  • Reduced load per participant
This will not be easy! Or quick! Covey’s “Effective vs. Efficient”

Blog Example
A community of 40 selected science bloggers, set up as an experiment in scientific communication

Google ScienceBlogs*

Blog Example
A community of 40 selected science bloggers, set up as an experiment in scientific communication

Blog Example
A community of 40 selected science bloggers, set up as an experiment in scientific communication
**Wiki Example**

Google

“wikipedia evidence-based medicine”

**Enables Community Input & Editing**

Evidence-based medicine

PBRNs – A useful human medicine model?

Primary care practice-based research networks: Working at the interface between research and quality improvement

http://www.annfammed.org/cgi/content/full/3/suppl_1/s12

- PBRNs are clarifying the reasons for disconnects between discovery and implementation, research and practice
- Stakeholders agree on their goals; apply their collective knowledge, skills, and resources to accomplish these goals
- PBRNs are evolving into learning communities, proving grounds for clinical problem solving and primary care improvement

**The way forward?**

1. Establish the structure to manage information exchange and translation
2. Assemble species x discipline interest groups and establish the communication structure within
3. Establish criteria for determining the important clinical questions
4. Determine the most important clinical questions
5. Perform systematic reviews on each to establish the state of evidence and identify the weak but critical evidence
6. Establish multi-group collaborative studies to generate strong evidence
7. Update the systematic reviews as evidence becomes available

I don’t have all the answers but | I believe that for the good of the profession the discussion must start. Our clients do (or soon will) expect nothing less!

**Evidence-based Veterinary Medicine:**

The best discipline intersection for clinical practice