Non-randomized trials that changed medical practice

First survey was performed in May 2000 by Ben Djulbegovic; estimated number of recipients ~1,500. Second survey of 1044 recipients of EVIDENCE-BASED-HEALTH list was performed by Paul Glasziou in November of 2003

The following list includes those trials of therapies which, according to the opinion of the members of the Evidence-Based Discussion Group, have demonstrated self-evident efficacy that most observers would agree about the truthfulness of the reported findings (as evident by the wide-spread acceptance of these treatments). That is, the effect of a given health care intervention is considered so large that overrides the combined effects of bias and random errors on the study's findings

When randomized trials (RCTs) may not be needed?

Some proposed criteria:

I Oxford/Sackett "All or none" criterion, which is met when all patients died before the [intervention] became available, but some now survive on it; or when some patients died before the [intervention] became available, but none now die on it. (see Oxford's Centre for Evidence Based Medicine level of evidence)

II Italian/Nino Cartabellota criteria:

All of the following criteria should be met (contributed by Nino Cartabellotta to Paul Glasziou): a) bad outcome of disease if untreated (high/very high control event rate), b) dramatic benefit of treatment (high relative risk reduction), c) acceptable side effects of treatment (high/very high number need to harm), d) no alternative treatment, e) convincing physiopathological basis

Arash Rashidian cited paper by Nick Black (World J Surg 1999;23:789-793) to provide the following criteria when RCT is not needed:

III Nick Black's criteria: Experimentation may be unnecessary, inappropriate, impossible, or inadequate when:

Unnecessary - when the effect is so dramatic that unknown confounding factors could be ignored, like immobilisation of fractured bones or treatment of diabetic coma with insulin. Inappropriate: 1. when the outcome is rare, 2. outcome happens far in the future and long follow-ups are required (e.g. loosening of artificial hip joints), 3. when randomization could reduce effectiveness (e.g. surgeons may be expert in one and not the others). Impossible: 1. clinicians refusal to participate [e.g. lack of equipoise (added by BD; see Current Oncology Reports 2001;3:389-95), 2. ethical considerations (e.g. cardiac
transplant vs. medical management (again, due to lack of equipoise-added by BD), legal obstacles, **Inadequate**: low external validity of many trials (e.g. in surgery).

IV “10 x rule” - data from non-RCTs can be trusted if the ratio of treatment effects between two alternative therapies > 10. In all other circumstances, the real treatment effects cannot be reliably separated from the effects of biases and random errors without employing RCT design. (See Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise BMJ 2007;334:349-351 http://www.bmj.com/cgi/content/full/334/7589/349

This is a work in progress and of potentially great importance (it can help us learn about effectiveness of our therapeutic innovative efforts). Please send your comments or information about trials (djulbebm@moffitt.usf.edu) that are not included in the list and that according to your opinion should have been included. In addition, we would welcome inclusion of any new trials that are deemed to meet above criteria.

Please note that not all listed articles have been reviewed; references are included as they were submitted to Ben Djulbegovic, who then compiled a list. Similarly, sources have not been provided for the number of examples/claims. Therefore, it is possible that some of the papers/examples included do not meet above stated criteria for a "trial that changed our practice."

We are interested in learning about achievements in all fields in medicine that can help us identify those great successes that changed medical practice. For example, an excellent recent summary on Achievements in Hematology in the Twentieth Century was published in Semin Hematol 1999;36 (supplement 7):1-132

If you know for any additional summary in other medical fields, please let us know.

**Endocrinology**

1. Insulin in treatment of diabetes mellitus
(a good example showing that when pathophysiology is worked out in details, an effective treatment can successfully be designed)


"It seems that Banting might have tried the stuff (orally) on himself first, in the great tradition of Hunter and, more recently Barry Marshall (Heliocbacter), and certainly made it available to a diabetic colleague before he gave it to a patient" (contributed by Konrad Jamrozik)

2. Thyroid hormone(s) in the treatment of hypothyroidism?
   3. thyroid extract for myxedema (cure)
   4. thyrostatics for thyrotoxicosis (cure)

   (another good example demonstrating that when pathophysiology is worked out in details, an effective treatment can successfully be designed)

   (Again, we would appreciate receiving any help in finding the original, first report on this revolutionary treatment)

5. steroids in the treatment of adrenal cortical hypofunction

   (another good example showing that when pathophysiology is worked out in details, an effective treatment can successfully be developed)

   (Again, we would appreciate receiving any help in finding the original, first report on this revolutionary treatment)

**Infectious diseases**


   [the first reports on the dramatic effect of penicillin in humans (5 patients were given treatment intravenously, 1 orally and 4 topically); this report has revolutionized modern medicine]

7. streptomycin for TB meningitis (return of consciousness and survival)
8. gancyclovir for CMV retinitis in AIDS (complete arrest of the disease)

**Oncology and Hematology**

(this phase II trial has established curative effect of cisplatin-based therapy in the treatment of testicular cancer)


   (this phase II trial has established a curative potential of MOPP chemotherapy in the treatment of Hodgkin's disease; this therapy was later found somewhat inferior against ABVD when tested in RCT; see "the list of RCT" that changed the practice)


   (this phase II trial has established curative effect of cladribine therapy in the treatment of hairy-cell leukemia)


   (this phase II trial has established high efficacy of B12 in the treatment of pernicious anemia)

13. Use of factor VIII and IX concentrates in hemophilia

   (another good example showing that when pathophysiology is worked out in details, an effective treatment can successfully be designed)

   (We would appreciate receiving any help in finding the original, first report on this revolutionary treatment)

14. Use of bone marrow transplantation in the treatment of hematologic malignancies

   An excellent review by ED Thomas,a "father" of BMT describing how BMT has become accepted form of treatment for the most of hematologic malignancies, particularly acute leukemias can be found in Semin Hematol 1999;36(suppl 7):95-103

15. Blood transfusion in humans

   another excellent example of development of the treatment based on the understanding of pathophysiological principles

   please help us find the original reference describing use of this revolutionary treatment in humans
17. Folic acid antagonist for treatment of acute leukemia
18. Steroids for treatment of lymphoid malignancies
19. Exchange transfusion for erythroblastosis fetalis
20. Streptokinase for myocardial infarction
21. Radiation therapy for Hodgkin's disease
22. Combination chemotherapy for acute lymphocytic leukemia in children
23. Prevention of Rh immunization
24. Central nervous system and combination therapy in childhood lymphocytic leukemia
25. Cytosine arabinoside and daunorubicin in acute nonlymphocytic leukemia
26. Antilymphocyte globulin with and without allogeneic bone marrow transplant for aplastic anemia
27. All-trans retinoic acid for acute promyelocytic leukemia

#9,12,13,15-26 cited in Lichtman MA et al. Hematology. Landmark papers of the twentieth century. Academic Press:San Diego, 2000. This remarkable book contains copies of the original case series+commentaries. Note that many treatments were later improved by further testing in RCTs, but they initial introduction in practice was based on dramatic effects noted in case series. A few of these interventions were introduced in practice after 1962, when the FDA act was passed requiring more rigorous testing in clinical trials in order to grant drug approval

28. Imatinib in treatment of CML (chronic myeloid leukemia)


   These 2 papers dramatically changed a contemporary practice for the treatment of CML, despite the fact that there is no data (as yet) that imatinib can cure CML. Nevertheless, use of allo-BMT-toxic but only known curative treatment for CML has dramatically decreased. This has been known as **Gleevec effect** (Gleevec is a brand name for imatinib). One should note that recently imatinib has also been compared to interferon and ara-C in a randomized trial, and was proven superior in terms of hematologic and cytogenetic response, tolerability, and the likelihood of progression to accelerated-phase or blast-crisis of CML (N Engl J Med 2003;348:994-1004)

29. vitamin C (citrus fruits) to treat scurvy ("**the fruit that changed the world**")
Tobi Lipman suggested this example. For wonderful description of this first attempt to perform "fair and unbiased" testing in therapeutics please see The James Lind Library

**Pulmonary Medicine**


"This article suggested that fenoterol was harmful and subsequently fenoterol virtually disappeared as an asthma drug in new zealand and possibly in other countries. This was hotly debated. Walter spitzer later did a cohort study in canada (saskatchewan) and claimed there was no difference between salbutamol and fenoterol on a dose for dose basis. Not sure who was right but fenoterol disappeared as there were clear (and safe?) alternatives eg salbutamol"

(contributed by Bruce Arroll)

**Urology**


The original article that spurred the debateTURP (trans-urethral resection of prostate) vs. open prostatectomy debate in the treatment of benign hyperplasia of prostate (BHP). One of the outcomes of that debate was confirmation of TURP as an established method of treating BHP. Concato and Feinstein in their non-randomized study(Transactions of the Association of American Physicians. 103:90-5, 1990.) strengthened the case for TURP. Based on these non-randomized observations TURP is now so widely used for the treatment of BHP

(contributed by Arindam Basu)

**Cardiovascular Medicine**

31. Defibrillation for ventricular fibrillation (and automated external defibrillators in cardiac arrest) (people lived!)

**Musculoskeletal**

32. total hip and kneed replacements
33. Closed reduction of fractures of long bones with deformity?
Neurology

34. cholinesterase inhibitors for myastenia gravis (immediate return of muscle power)

Psychiatry

35. antipsychotics (e.g. chlorpromazine) in schizophrenia and related disorders?

Surgery

36. Appendectomy in perforated appendicitis
37. sewing up wounds
38. ether anesthetic
39. sterile conditions for surgery
40. cholecystectomy for symptomatic gallstones
41. hip replacement for fracture next of femur (high death rates with bed rest alone

items #27,#28 contributed by Cindy Farquhar

Other fields

42. some organ transplantation (e.g. liver transplant in fulminant acute hepatitis
43. some antidotes in poisoning
44. recompression for decompression illness
45. supine sleeping to prevent sudden death syndrome

"It needed a RCT in 1946 when the US and UK were more-or-less in equipoise. However, it didn't need a RCT by 1986 because the strong evidence from observational studies:i) high relative effect (from case control, cohort and time series studies),ii) rare but serious consequences of not treating, iii) no evidence of adverse effects. (contributed by Ruth Gilbert

Send all comments regarding this list to:

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