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Journal of Biomedical Research

Bo Cui, MD, PhD

Executive Deputy Editor-in-Chief

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The scientific impact of nations

What different countries get for their research spending.

David A. King

The ability to judge a nation's scientific standing is vital for the governments, businesses and trusts that must decide scientific priorities and funding. In this paper I analyse the output and outcomes from research investment over the past decade, to measure the quality of research on national scales and to set it in an international context. There are many ways to evaluate the quality of scientific research, but few have proved satisfactory. My analysis updates and extends the groundbreaking work by May[1], which covered 1981–94, and draws on a study of 1993–2002 commissioned by

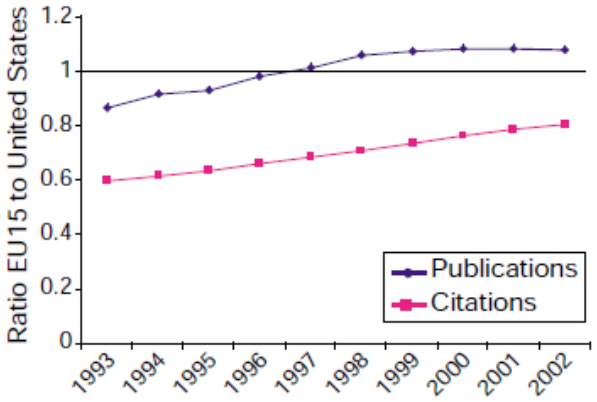
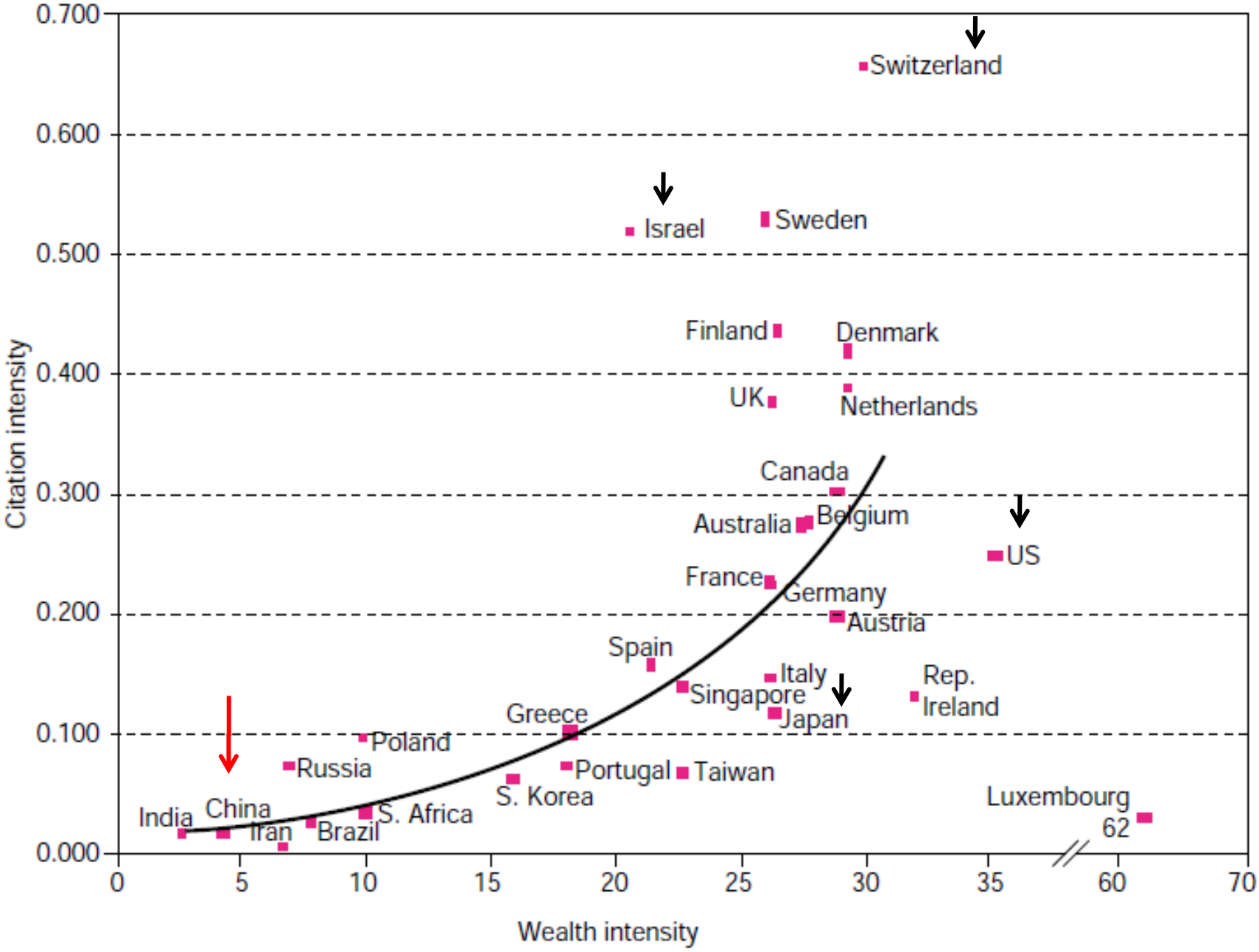


Figure 1 Comparing Europe with the United States. Ratio of the publications and citations of the 15 European Union countries in the comparator group (EU15) to the United States on ISI databases in 1993–2002. The EU15 total contains some duplication because of papers jointly authored between countries in the EU group. Counts for papers and citations are totals for country (or group) for the stated year.

Austria, Belgium, Brazil, *Canada*, China, Denmark, Finland, *France*, *Germany*, almost as many papers and Germany is closing the gap in citations.

Nature. 2004 Jul 15;430(6997):311-6.



Nature. 2004 Jul 15;430(6997):311-6.

Knowledge, networks and nations

Global scientific collaboration in the 21st century

EXCELLENCE IN SCIENCE

THE ROYAL SOCIETY

Knowledge, Networks and Nations: Global scientific collaboration in the 21st century

RS Policy document 03/11
Issued: March 2011 DES2096

ISBN: 978-0-85403-890-9

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Monday 28 March 2011 22.00 BST

China poised to overhaul US as biggest publisher of scientific papers

Royal Society report shows China pushing UK into third place in scientific publishing and predicts it will soon surpass the US

Figure 1.1. **Proportion of global publication authorship by country**[17]

The top ten producing countries in each period are shown. **Fig a.** *1999-2003.* **Fig b.** *2004-2008*

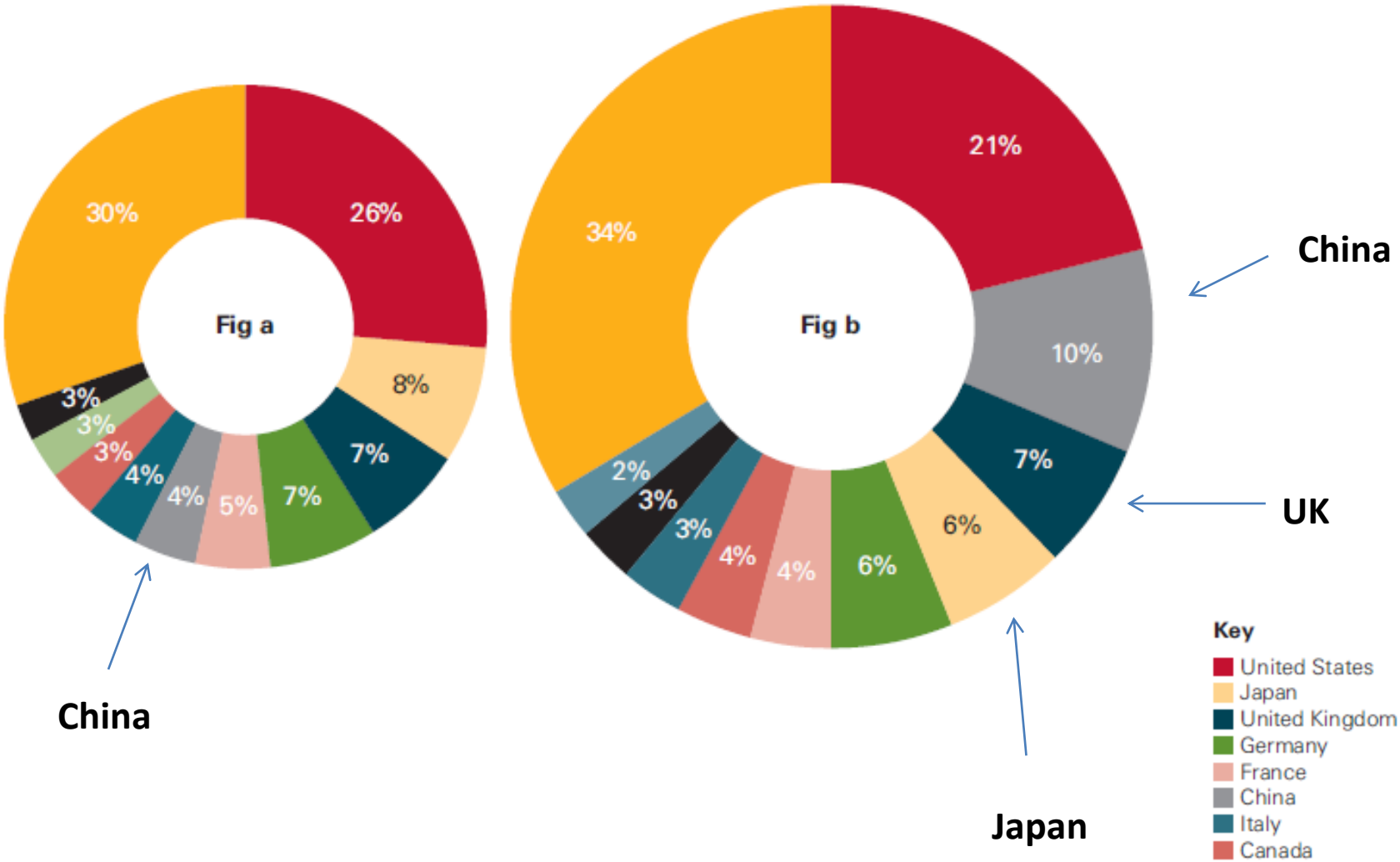


Figure 1.5. **R&D spending, selected countries 2000–2015;**
the dotted lines indicate projections, based on announced targets.[151]

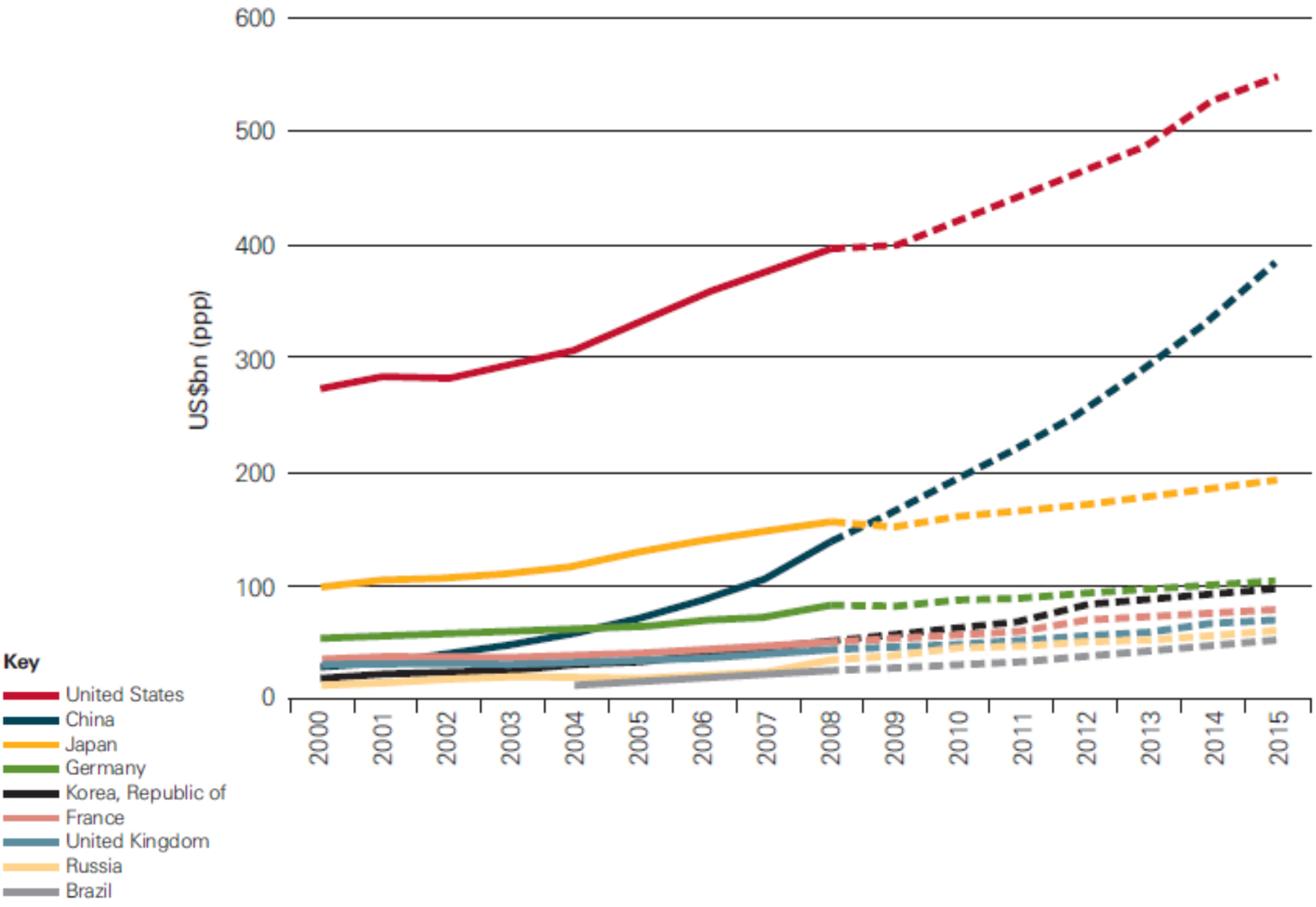
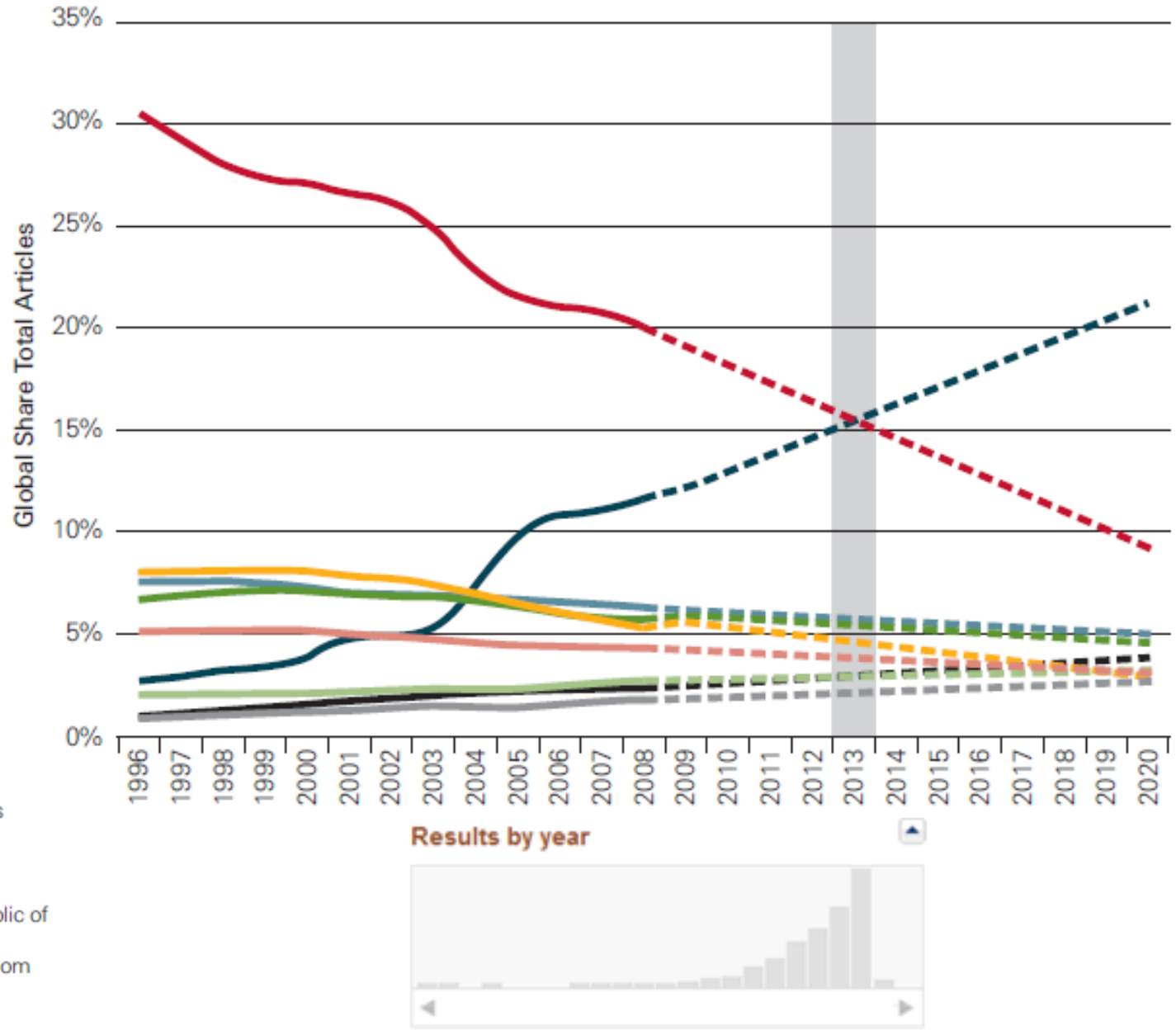


Figure 1.6. **Linear extrapolation of future publication trends.**[155]

The dotted lines indicate projections



Knowledge, Networks and Nations: Global scientific collaboration in the 21st century

RS Policy document 03/11
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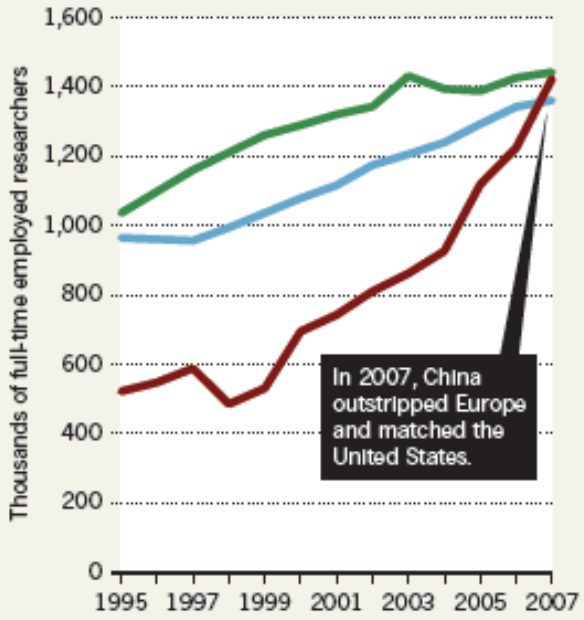
EASTERN PROMISE

Chinese science is flourishing, but still has a way to go.

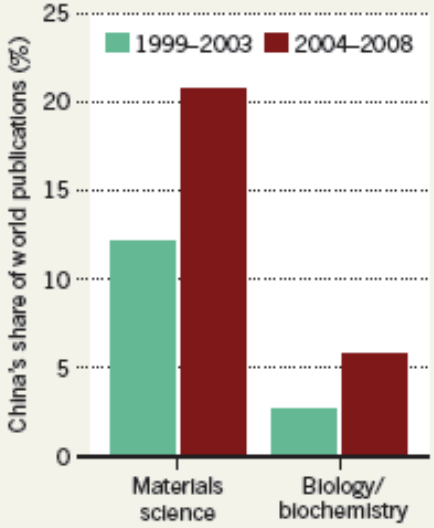
POPULATION BOOM

The number of scientists has grown faster in China than elsewhere.



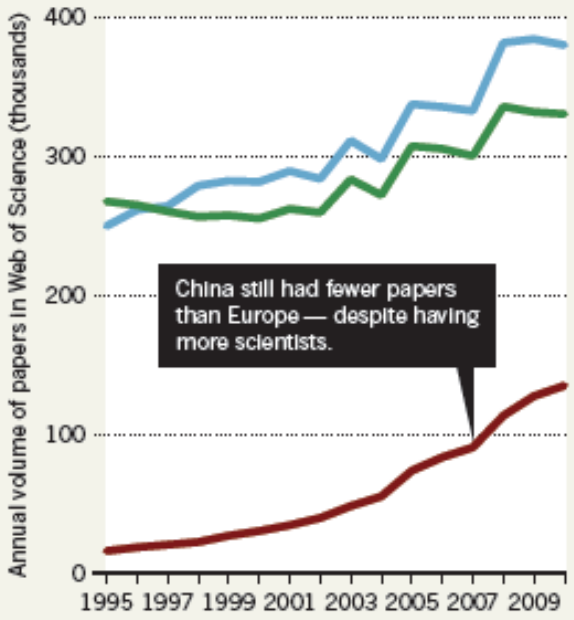
MATERIAL WORLD

Progress in biology lags behind that in materials science.



PAPER TRAIL

Scientific publications have increased around the world in the past decade.



SOURCES (L TO R): OECD; WEB OF SCIENCE; WEB OF SCIENCE

Figure 1.4. **Top 20 publishing cities 2004–2008, and their growth since 1996–2000.**[126]

Knowledge, Networks and Nations: Global scientific collaboration in the 21st century
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Effective Writing for Biomedical Publications

Bo Cui, MD/PhD

01/09/2013

From the title to the references
From submission to revision

“The man of science appears to be the only person who has something to say just now, and the only man who does not know how to say it.”

– Sir James Barrie

Ways of help for writing a scientific paper

- Writing workshops for physicians and scientists (e.g. UCSF, UBC)
- Writing seminars
- Peer scientists
- A friend with adequate education who is not a scientist
- Books/articles about writing scientific papers
- Paid editing service
- In-house editing service (e.g. Mayo Clinic, Univ. of Tokyo)

Reasons for publications

Questions to ask yourself before submitting your manuscript:

- Have you really done anything new or interesting?
- Is there anything challenging in your work?
- Is the work related to a currently hot topic?
- Have you provided solutions to any difficult problems?

Determine Your Article Types

- Editorial
- Original article
- Review article
- Short paper
- Case report
- Letter to the editor
- Personal views
- Special communications

Determine Your Article Types

- Editorial
- Original article
- Review article
- Short paper
- Case report
- Letter to the editor
- Personal views
- Special communications

- It is a scientific report of the results of *original* basic or clinical research.

- Original :

  1) of, relating to, or constituting an origin or beginning;

  2) not secondary, derivative, or imitative;

  3) being the first instance or source from which a copy, reproduction, or translation is or can be made;

  4) independent and creative in thought or action .

Merriam Webster Dictionary

Determine Your Article Types

- Editorial
- Original article
- Review article
- Short paper
- Case report
- Letter to the editor
- Personal views
- Special communications

- It communicates essential sources of information about a rare or unreported feature, condition, complication, or intervention.
- It expands our knowledge or spawns new research.
- It may lead to better patient care.

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

The Index Case for the Fungal Meningitis Outbreak in the United States

April C. Pettit, M.D., M.P.H., Jonathan A. Kropski, M.D.,
Jessica L. Castilho, M.D., M.P.H., Jonathar
Carol A. Rauch, M.D., Ph.D., Bret C. Mobley,
Steven S. Spires, M.D., and Meredith E

SUMMARY

Persistent neutrophilic meningitis presents a diagı
ferential diagnosis is broad and includes atypical
case of persistent neutrophilic meningitis due to A
competent man who had no evidence of sinopulr
epidural glucocorticoid injection was identified as
organism into the central nervous system, and th
health department.

CASE REPORT

A man in his 50s with a history of degenerative lumbar-disk and joint disease presented with headache and neck pain that had become progressively worse over the course of 8 days. The associated symptoms included nausea, malaise, fatigue, chills, and decreased appetite. The patient reported no fevers, rash, photophobia, or vision changes. Four weeks before presentation, he had received the latest in a series of epidural injections of methylprednisolone for low back pain. The patient

REVIEW ARTICLE

CURRENT CONCEPTS

Fungal Infections Associated with Contaminated Methylprednisolone Injections — Preliminary Report

Carol A. Kauffman, M.D., Peter G. Pappas, M.D., and Thomas F. Patterson, M.D.

Determine Your Article Types

- Editorial
- Original article
- Review article
- Short paper
- Case report
- Letter to the editor
- Personal views
- Special communications

- It is usually a commentary concerning an article recently published in a journal.
- It can also be a very concise report on novel findings or cases.

CORRESPONDENCE

Sirolimus and Skin-Cancer Prevention in Kidney Transplantation

TO THE EDITOR: With regard to the study by Euvrard et al. (July 26 issue),[1] which investigated options for decreasing the burden of disease in kidney-transplant recipients: I think the dichotomous conclusion that switching to an immunosuppressive drug with potential antineoplastic properties[2] to reduce the risk of secondary skin cancer is incomplete.

Important information regarding previous baseline immunosuppression for earlier transplantation was included for both treatment groups (i.e., before the study period). No information was given regarding primary renal disease and related therapies, which could have included long episodes of treatment with immunosuppressive agents, including calcineurin inhibitors, prednisone, azathioprine, and many other options.

Furthermore, no distribution of age was given for the first occurrence of skin cancer, which is in general more prevalent in the elderly. A higher proportion of elderly patients and recurrent skin cancer in either group could have been important factors in choosing the type of immunosuppressive therapy.

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No potential conflict of interest relevant to this letter was reported.

1. Euvrard S, Morelon E, Rostaing L, et al. Sirolimus and skin-cancer tumor burden in kidney-transplant recipients. Reduction of immunosuppression has been increasingly considered in the treatment of transplant recipients with skin cancer.[1]

The influence of end-stage kidney disease per se on the occurrence of skin cancer remains unclear.[2] Our study did not have the power to allow us to analyze the influence of various kidney diseases on the occurrence of skin cancer. Although we did not record immunosuppression before transplantation, we think that exposure to immunosuppressive medications before transplantation was probably very small as compared with the long-term exposure to calcineurin inhibitors after transplantation that patients received by the time of the occurrence of skin cancer. Though age remains one of the main risk factors for squamous-cell carcinoma of the skin, no age difference at the occurrence of the first squamous-cell carcinoma was observed in our patients (59 years in both groups).

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sylvie.euvrard@numericable.fr

Evidence of Adult Lung Growth in Humans

TO THE EDITOR: Butler et al. (July 19 issue)[1] describe a 48-year-old woman in whom apparent-diffusion-coefficient data derived from helium-3 magnetic resonance imaging (MRI) suggested new (versus hyperexpanded) alveoli in regions of new lung growth. This patient also had improved pulmonary function 15 years after pneumonectomy. The helium-3 apparent-diffusion-coefficient maps and posterior–anterior apparent-diffusion-coefficient differences were not reported but have been previously evaluated in childhood lung development[2] and chronic obstructive pulmonary disease.[3] It is important to note the patient's history of smoking because the heterogeneous and reduced alveolar depth measurements reported may in fact indicate mild emphysema.

We report a heterogeneous apparent diffusion coefficient in another former smoker. Seven years after lobectomy, this 60-year-old patient did not have improved pulmonary function (Fig. 1). The apparent diffusion coefficient was age-appropriate[4] for a person who had never smoked, although an elevated apparent diffusion coefficient was observed in the right upper lung with the posterior–anterior apparent-diffusion-coefficient gradient reversed as compared with previous findings.[3] Although we cannot rule out new lung growth in this older patient, these findings are consistent with alveolar expansion or emphysema. We think apparent diffusion coefficients and their regional differences are important when evaluating lung growth because MRI-derived alveolar dimensions based on the model and assumptions of Haefeli-Bleuer and Weibel[5] may not completely explain abnormal morphologic features in the lungs after surgery in former smokers.

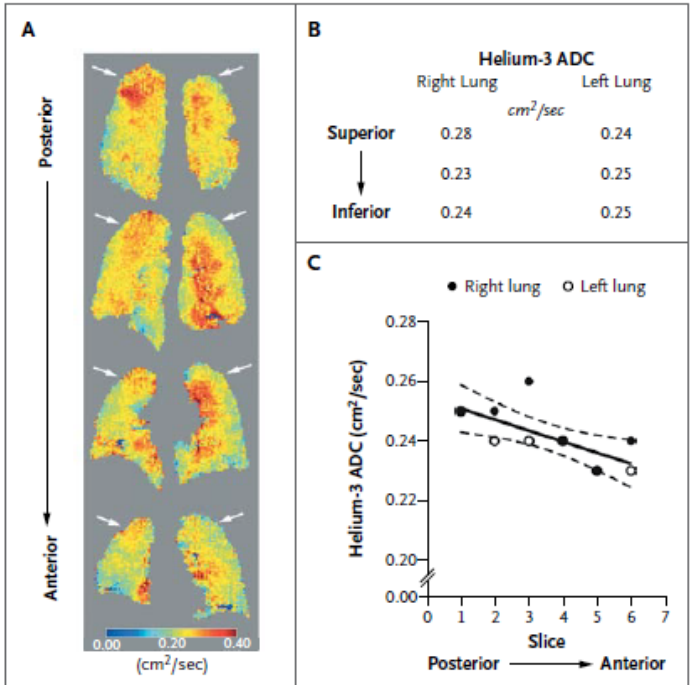

Figure 1. Heterogeneous Apparent Diffusion Coefficient in a Former Smoker.
Panel A shows four central coronal slices obtained with helium-3 magnetic resonance imaging in a 60-year-old female former smoker with a 44-pack-year history who had quit smoking 8 years previously and had undergone lobectomy of the right upper lung 7 years previously. The forced expiratory volume in 1 second (FEV_1) was 76% of the predicted value, the ratio of FEV_1 to forced vital capacity was 0.98, and the carbon monoxide diffusing capacity was 86% of the predicted value. The white arrows highlight areas with a greater apparent diffusion coefficient (ADC) in the right upper lung than in the left upper lung. Panel B shows helium-3 ADC values from the superior portions of the lungs to the inferior portions. Panel C shows posterior-to-anterior regions of interest in the right and left lung ($r=0.71$, $P=0.01$).

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Grace Parraga, Ph.D.

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No potential conflict of interest relevant to this letter was reported.

Components of an Original Research Paper

- Title
- Authors
- Abstract
- Keywords
- Introduction
- Materials and Methods
- Results
- Discussion
- Acknowledgement
- References

- A good title should clearly and succinctly describe the content of the paper.
- It is also the advertisement for the paper.
- It should be accurate as indexing databases use key words to identify relevant articles.
- Avoid using technical jargons and abbreviations.

Writing an effective title

- An title should reflect the central message of the paper.
- An title allows a reader to decide to further read the paper.

- Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and without HIV infection.
- Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas.

Writing an effective title

- Changes of pulmonary glucocorticoid receptor and phospholipase A2 in sheep with acute lung injury after high dose endotoxin infusion.
- Stem cells downregulate the elevated levels of tissue plasminogen activator in rats after spinal cord injury.

Components of an Original Research Paper

- Title
- Authorship
- Abstract
- Keywords
- Introduction
- Materials and Methods
- Results
- Discussion
- Acknowledgement
- References

- Make sure all those who have made significant contributions to the work are recognized.
- An author has approved the final version of the paper and will publicly defend the data and conclusions.
- The corresponding author is listed as the last author.

Components of an Original Research Paper

- Title
- Authors
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- Discussion
- Acknowledgement
- References

- It is an essential but independent part of a paper.
- It has a word limit.
- It should be clear, concise and to the point.
- Limit use of abbreviations.
- Usually it is written last.
- Consult the journal for instruction for writing the abstract.

Writing an effective abstract

- State the principal objectives and scope of the investigation.
- Describe the methods used.
- Summarize the results.
- State the principal conclusions.
- Be brief (250 words maximum).
- Avoid abbreviations and jargon.

Components of an Original Research Paper

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- Discussion
- Acknowledgement
- References

- It is the label of your work.
- Be accurate and relevant.
- They are used by abstracting and indexing services to identify the paper.

Components of an Original Research Paper

- **Title**
- **Authors**
- **Abstract**
- **Keywords**
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- Results
- Discussion
- Acknowledgement
- References

- **Make them easy for indexing and searching (informative, attractive, and effective)**

J Biomed Res. 2011 Mar;25(2):111-119.

A Functional Type I Interferon Pathway Drives Resistance to Cornea Herpes Simplex Virus Type 1 Infection by Recruitment of Leukocytes.

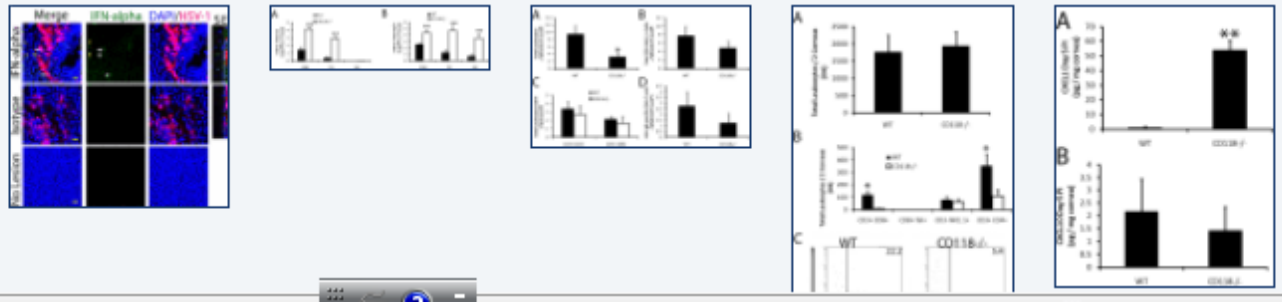
Conrady CD, Jones H, Zheng M, Carr DJ.

Departments of Microbiology, Immunology, The University of Oklahoma Health Science Center, Oklahoma City, Oklahoma, 73104, USA.

Abstract

Type I interferons are critical antiviral cytokines produced following herpes simplex virus type-1 (HSV-1) infection that act to inhibit viral spread. In the present study, we identify HSV-infected and adjacent uninfected corneal epithelial cells as the source of interferon-α. We also report mice deficient in the A1 chain of the type I IFN receptor (CD118(-/-)) are extremely sensitive to ocular infection with low doses (100 PFU) of HSV-1 as seen by significantly elevated viral titers in the cornea compared to wild type (WT) controls. The enhanced susceptibility correlated with a loss of CD4(+) and CD8(+) T cell recruitment and aberrant chemokine production in the cornea despite mounting an adaptive immune response in the draining mandibular lymph node of CD118(-/-) mice. Taken together, these results highlight the importance of IFN production in both the innate immune response as well as eliciting chemokine production required to facilitate adaptive immune cell trafficking.

PMID: 21709805 [PubMed] PMCID: PMC3119485 Free PMC Article



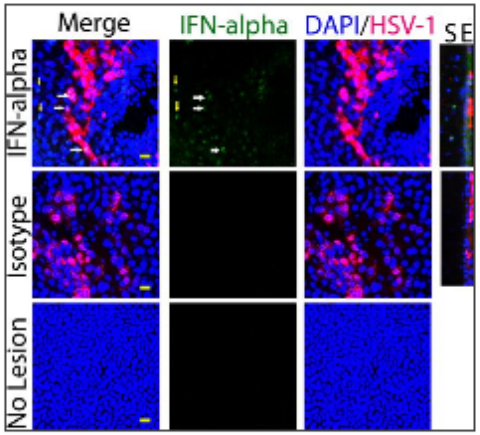


Figure 1
Expression of IFN-α by corneal epithelial cells following HSV-1 infection

Anesthetized wild type WT mice (n = 8 / stain) were infected with 1,000 PFU / cornea HSV-1. At day 3 PI, corneas were harvested, fixed, and stained for HSV-1 (red), IFN-α (green), and cell nuclei (blue). White arrows highlight infected cells expressing IFN-α, while yellow arrows indicate non-infected, IFN-α producing cells. The top panel indicates IFN-α staining at sites of infection, the middle images are of IFN-α isotype controls, and the bottom pane is IFN-α staining at uninfected sites. On the far right are 3D reconstructions of the corneas on the left in which the top picture indicates IFN-α staining (in green), while the lower image is the isotype control. Images are representative of four independent experiments (2 corneas / group / experiment). Red represents HSV-1 antigen expression. S, corneal stroma; E, corneal epithelium, Yellow bar, 50 μm.

A Functional Type I Interferon Pathway Drives Resistance to Cornea Herpes Simplex Virus Type 1 Infection by Recruitment of Leukocytes
J Biomed Res. 2011 March;25(2):111-119.

Writing an effective introduction

- Title
- Authors
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- References

- Provide rationale for current study.
  – What gap in knowledge did you try to fill?
  – What controversy did you try to resolve?
- State the aim of study
- May briefly state study group, design and methods used, why they are better than in previous studies
- May state principal result/conclusion (?)

Writing an effective introduction

- The authors should provide background information broad enough to allow readers to understand the current state of the art but also specific enough to allow readers to see why the authors want to address a specific research question.

- Stay focused. The most common problem in introduction is lack of focus.

- **This is a time to show your sound scientific judgment.**
- Start from a large area of knowledge to the specific research question
- Avoid a detailed history of the subject.
- Use references intelligently, not just any reference one can get hold of. Cite important original major publications that your research is based upon.
- Do not include detailed results from previous studies.

Writing an effective introduction

- The authors should provide background information broad enough to allow readers to understand the current state of the art but also specific enough to allow readers to see why the authors want to address a specific research question.
- Stay focused. The most common problem in introduction is lack of focus.

- **This is a time to show your sound scientific judgment.**
- A well-written introduction assists both the reader and the reviewer by moving the reader from what is known about a topic to what is unknown..
- Start from a large area of knowledge to the specific research question.
- Avoid a detailed history of the subject.
- Do not include detailed results from previous studies.

Writing an effective introduction

- Provide the rationale for your study.
- State the aim of your study.
- Define abbreviations when they first appear and use them sparingly.

- Identify the gap in the current framework of knowledge.

  -what gap would like to fill?

  -what problem would like to solve?

Writing an effective introduction

- Provide the rationale for your study.
- State the aim of your study.
- Define abbreviations when they first appear.

- To determine whether . . .
- To determine which . . .
- The purpose of this study was . . .
- Therefore, we tested the hypothesis that . . .
- This report describes experiments designed to determine whether . . .

Writing an effective introduction

- Provide the rationale for your study.
- State the aim of your study.
- Define abbreviations when they first appear and use them sparingly.

Writing an effective introduction

- Use references intelligently, not just any reference one can get hold of. Cite important original major publications that your research is based upon. But always refer to your previous work if you have.

- Use the most recent, most direct, most succinct, and the most relevant references. Indiscriminate use of too many references suggests that the author is not knowledgeable in the field and lack judgment in failing to choose the most important and relevant studies on the topic.

Writing an effective introduction

在我九十岁那天，我决定送给自己个礼物: 和年轻的处女过一夜.....

Gabriel García Márquez: “Memorias de mis putas tristes”

Writing an effective introduction

"We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological importance."

Watson JD, Crick FHC. A structure for deoxyribose nucleic acid. *Nature 1953;171:737-8*

Writing an effective introduction

Central nervous system (CNS) synapses are complex cell-cell adhesions between neurons. Their establishment requires an interaction between axons and dendrites, accompanied by the appositional organization of pre- and postsynaptic specializations. Several neuronal cell surface molecules and secreted signals have been shown to be involved in processes that lead to synaptic organization and maturation (Fox and Umemori, 2006), but **molecules that regulate the formation of initial synaptic adhesions remain poorly understood.** Accumulating evidence from our lab and others has shown that astrocytes play active roles in the formation of synapses (Eroglu et al., 2008). We have previously identified **thrombospondins (TSP)** as a necessary and sufficient synaptogenic signal secreted by astrocytes that increases synapse number (Christopherson et al., 2005). TSP is present in astrocyte-conditioned media (ACM) and is responsible for the ability of astrocytes to increase synapse number in vitro (Christopherson et al., 2005). TSPs are also important for synapse formation in vivo. *TSP1/2*-deficient mice have a significant decrease in the number of excitatory synapses. TSP1 and 2 are expressed during early postnatal ages, when the majority of synapses are forming, and these proteins are absent from the adult brain when the amount of excitatory synaptogenesis is significantly reduced (Christopherson et al., 2005). Upon injury to the CNS, TSP1/2 levels are upregulated, and lack of TSP1/2 impairs synaptic and functional recovery from stroke (Liauw et al., 2008).

The authors move from what is known

to what is unknown.

Define abbreviations.

Writing an effective introduction

- TSP is able to promote synaptic adhesion and initiate the events that lead to the establishment of pre- and postsynaptic specializations. Interestingly, these TSP-induced synapses are ultrastructurally identical to fully developed synapses and are presynaptically active but postsynaptically silent because of the lack of surface AMPA receptors. Astrocytes secrete a second unrelated signal that is able to convert these silent synapses into fully active ones (Christopherson et al., 2005) (N.J.A. and B.A.B. unpublished data).
- TSPs are large oligomeric, multidomain, extracellular matrix proteins that have been previously shown to play important roles in cell attachment, cell migration, cytoskeletal dynamics, and angiogenesis (Bornstein et al., 2004). TSP mediates these functions via its interaction with various cell surface receptors through specific domains (Adams and Lawler, 2004). **We hypothesized that TSPs induce synapse formation by interacting with a neuronal cell-surface receptor.** Here, we show that TSPs mediate synaptogenesis through their epidermal growth factor (EGF)-like domains, common to all TSP isoforms. Using this domain information, we identified the gabapentin receptor α2δ-1 as the TSP receptor involved in synapse formation.

- Hypothesis generating
- State principal finding

Writing an effective introduction

The purpose of the introduction is to introduce the topic and engage the readers.

Components of an Original Research Paper

- Title
- Authors
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- Discussion
- Acknowledgement
- References

- This section explains how you have obtained your study results.

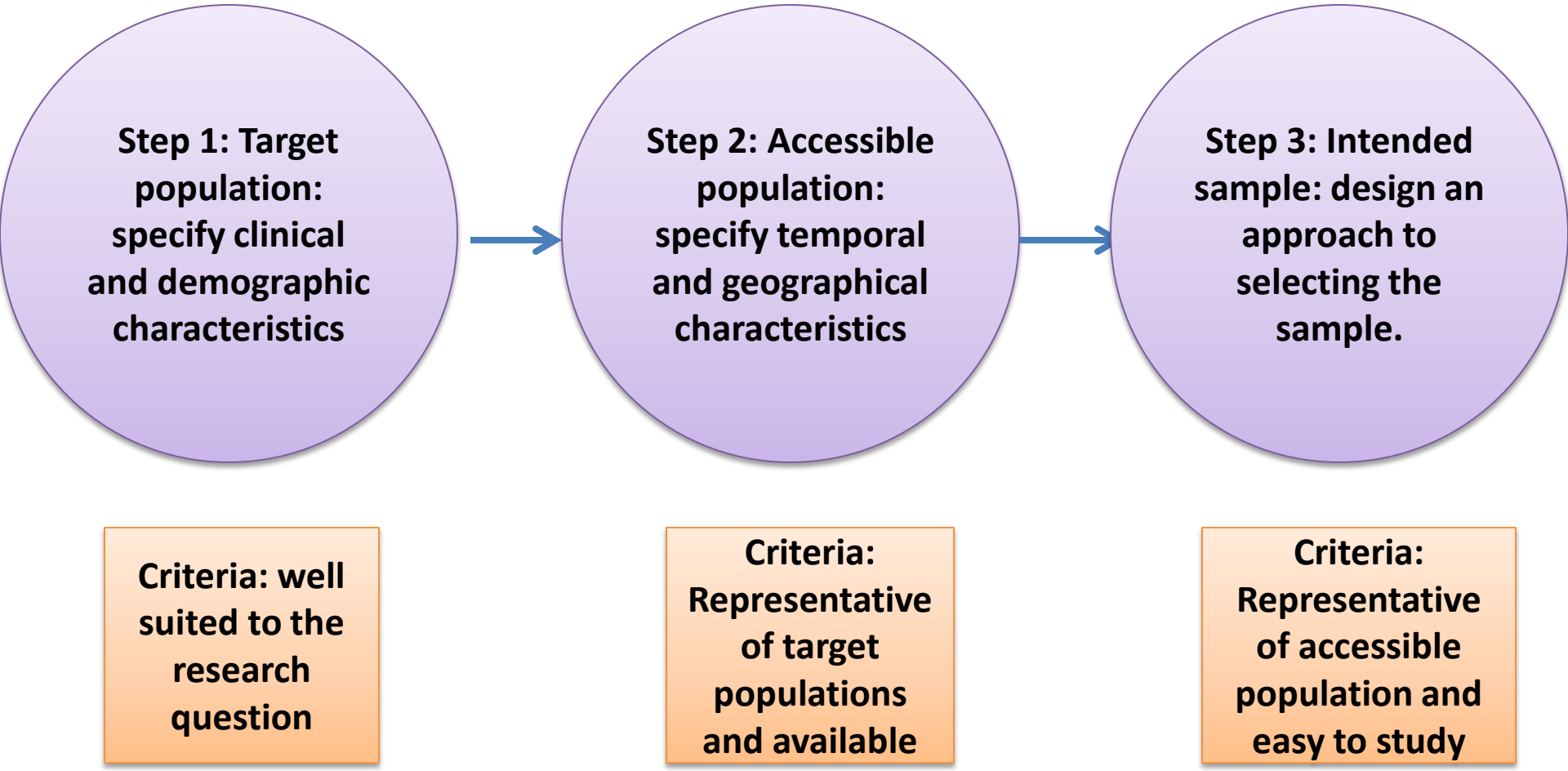
  -What has been done?

  -What did you look for?

  - How was it done?

- For established methods, just provide a reference.
- For modified methods, provide sufficient details.
- The methods (results) should be reproducible.

Designing Clinical Research



Designing Clinical Research

- The choice of design depends on the goal of the trial.

- **Proper design is critical; analysis cannot rescue improper design.**

Designing Clinical Research

VOLUME 24 · NUMBER 31 · NOVEMBER 1 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Study of Docetaxel and Cisplatin Plus Fluorouracil Compared With Cisplatin and Fluorouracil As First-Line Therapy for Advanced Gastric Cancer: A Report of the V325 Study Group

Eric Van Cutsem, Vladimir M. Moiseyenko, Sergei Tjulandin, Alejandro Majlis, Manuel Constenla, Corrado Boni, Adriano Rodrigues, Miguel Fodor, Yee Chao, Edouard Voznyi, Marie-Laure Risse, and Jaffer A. Ajani

From the University Hospital Gasthuisberg, Leuven, Belgium; N.N. Petrov Research Institute of Oncology, St Petersburg; N.N. Blokhin Cancer Research Center; Russian Scientific Centre of Radiology, Moscow, Russia; Fundación Arturo López Pérez; Hospital Clinico Universidad de Chile, Santiago, Chile; C.H. de Pc Spain; Arcispedal Reggio Emilia, Ita Universidade de Portugal; Taipei V Hospital, Taipei, Taiwan; sanofi aventis, Antony, France; and The University of

A B S T R A C T

Purpose

In the randomized, multinational phase II/III trial (V325) of untreated advanced gastric cancer patients, the phase II part selected docetaxel, cisplatin, and fluorouracil (DCF) over docetaxel and cisplatin for comparison against cisplatin and fluorouracil (CF; reference regimen) in the phase III part.

Conclusion

Adding docetaxel to CF significantly improved TTP, survival, and response rate in gastric cancer patients, but resulted in some increase in toxicity. Incorporation of docetaxel, as in DCF or with other active drug(s), is a new therapy option for patients with untreated advanced gastric cancer.

5 mg/m^2 and cisplatin 75 s or cisplatin 100 mg/m^2 (day 1) plus fluorouracil 1,000 mg/m^2/d (days 1 to 5) every 4 weeks. The primary end point was time-to-progression (TTP).

Designing Clinical Research

VOLUME 24 · NUMBER 31 · NOVEMBER 1 2006

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase III Study of Docetaxel and Cisplatin Plus Fluorouracil Compared With Cisplatin and Fluorouracil As First-Line Therapy for Advanced Gastric Cancer: A Report of the V325 Study Group

Conclusion
Adding docetaxel to CF significantly improved TTP, survival, and response rate in gastric cancer patients, but resulted in some increase in toxicity. Incorporation of docetaxel, as in DCF or with other active drug(s), is a new therapy option for patients with untreated advanced gastric cancer.

A prospective, randomized phase III study of docetaxel plus 5-fluorouracil and cisplatin compared with cisplatin and 5-fluorouracil in chemotherapy-naive Chinese patients with advanced or locally recurrent gastric cancer

Running head: Docetaxel plus 5-fluorouracil and cisplatin for advanced gastric cancer

Designing Clinical Research

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Running head: Docetaxel plus 5-fluorouracil and cisplatin for advanced gastric cancer

Conclusion

The modified DCF regimen significantly improved PFS, response rate and TTF of Chinese advanced gastric cancer patients, conferring a favorable risk benefit ratio in previously untreated Chinese patients.

Utilizing existing databases

- Secondary data analysis

- Previous research studies: collect more data than PI can analyze and some interesting findings go unnoticed.
- -Large regional and national data sets
- Tumor registries
- Administrative and clinical databases: useful for studies to evaluate patterns of utilization and clinical outcomes of medical treatment

Utilizing existing databases

- Secondary data analysis

- Senior colleagues
- Databases at home institutions
- Databases at other institutions
- Obtain permission and be specific about what information is sought

JAMA The Journal of the American Medical Association

August 19, 1998, Vol 280, No. 7 >

The Heart and Estrogen/progestin Replacement Study (HERS)

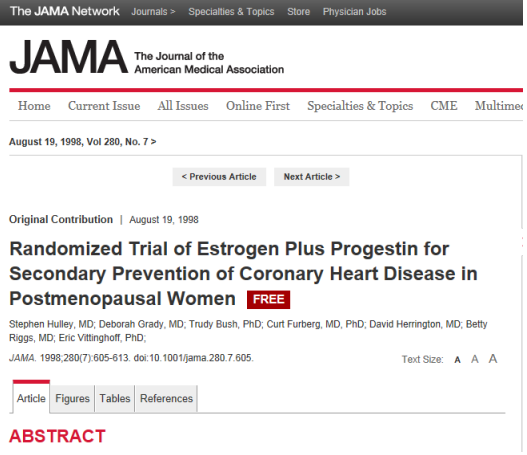
Original Contribution | August 19, 1998

Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women FREE

Stephen Hulley, MD; Deborah Grady, MD; Trudy Bush, PhD; Curt Furberg, MD, PhD; David Herrington, MD; Betty Riggs, MD; Eric Vittinghoff, PhD;

JAMA. 1998;280(7):605-613. doi:10.1001/jama.280.7.605.

ABSTRACT

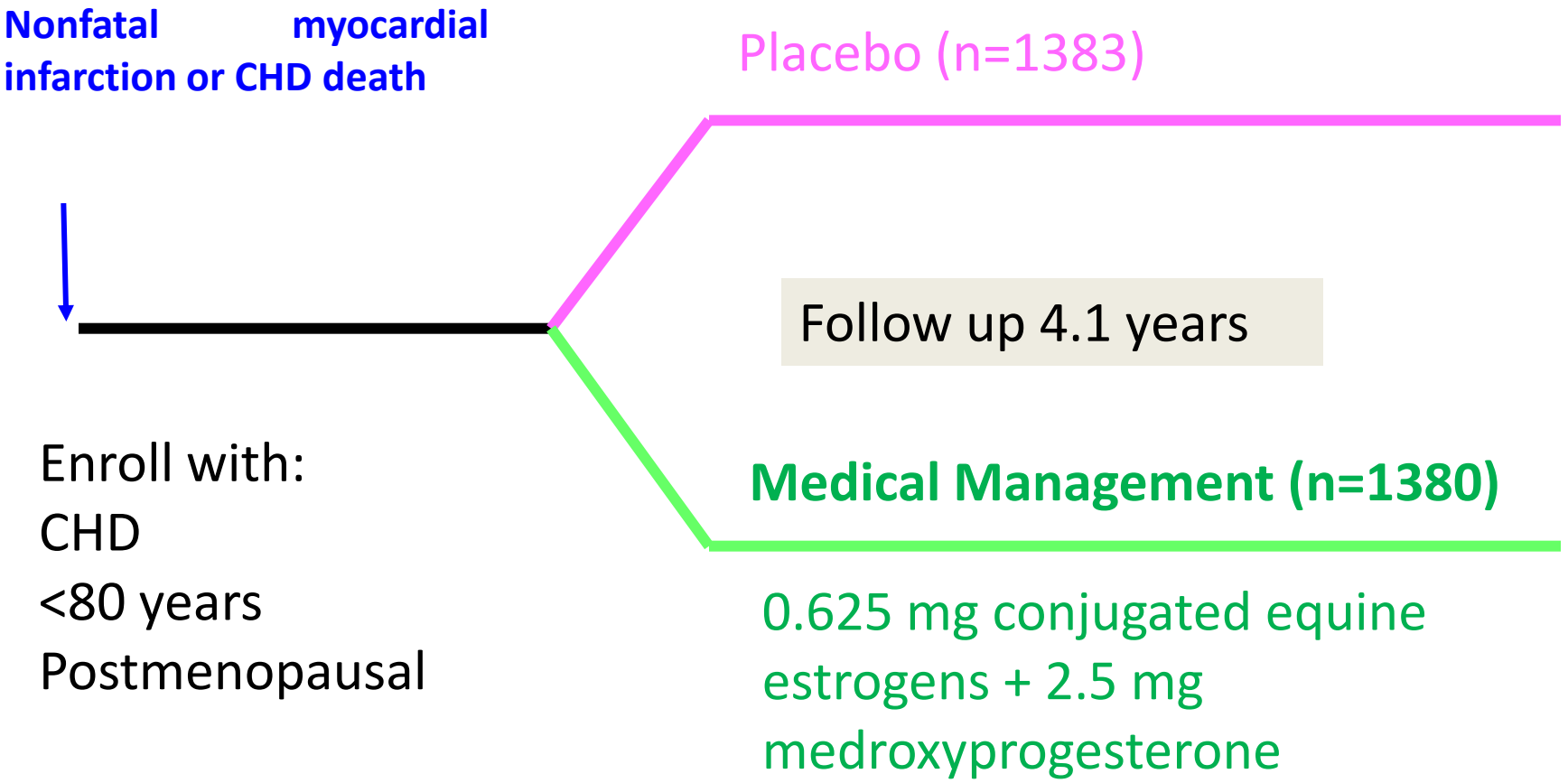


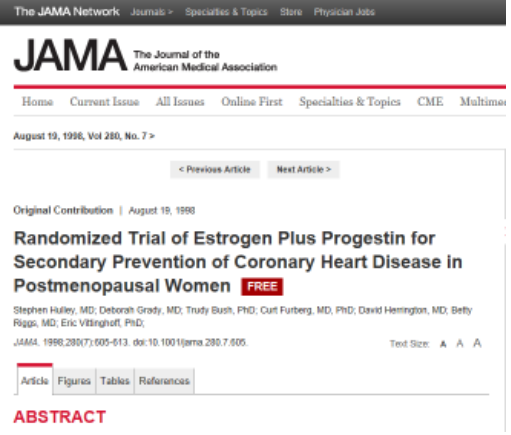
The Heart and Estrogen/progestin Replacement Study (HERS)

The study question:

Does estrogen plus progestin therapy alters the risk for CHD events in postmenopausal women with established coronary disease?

The Study Design

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Original Contribution | August 19, 1998

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Article Figures Tables References

ABSTRACT

Table 3.—Outcomes by Treatment Group and Year Since Randomization*

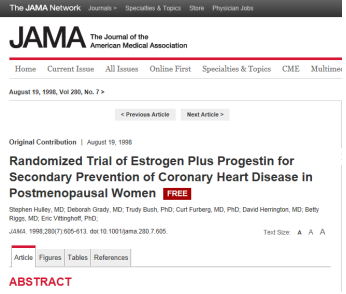
Outcome and Period	Estrogen-Progestin No.	Estrogen-Progestin Rate†	Placebo No.	Placebo Rate†	RH (95% CI)	P Value‡
Primary CHD event§						
Year 1	57	42.5	38	28.0	1.52 (1.01-2.29)	
Year 2	47	37.0	48	37.1	1.00 (0.67-1.49)	.009
Year 3	35	26.8	41	33.1	0.87 (0.55-1.37)	
Years 4 and 5	33	23.0	49	34.4	0.67 (0.43-1.04)	
Nonfatal myocardial infarction						
Year 1	42	31.3	29	21.4	1.47 (0.91-2.36)	
Year 2	34	26.8	37	28.6	0.94 (0.59-1.49)	.01
Year 3	20	16.5	29	23.4	0.70 (0.40-1.24)	
Years 4 and 5	20	13.9	34	23.9	0.58 (0.34-1.02)	
CHD death						
Year 1	17	12.5	11	8.0	1.56 (0.73-3.32)	
Year 2	19	14.4	13	9.7	1.48 (0.73-2.99)	.34
Year 3	18	14.0	16	12.3	1.14 (0.58-2.24)	
Years 4 and 5	17	11.0	18	11.6	0.95 (0.49-1.84)	
Unstable angina or coronary revascularization¶						
Year 1	101	77.1	94	71.1	1.08 (0.82-1.44)	
Year 2	52	43.3	85	70.6	0.61 (0.43-0.87)	.42
Year 3	69	61.9	56	50.5	1.22 (0.86-1.74)	
Years 4 and 5	47	36.6	67	54.2	0.67 (0.46-0.98)	
Venous thromboembolic event						
Year 1	13	9.6	4	2.9	3.29 (1.07-10.08)	
Year 2	8	6.1	2	1.5	4.09 (0.87-19.27)	.28
Year 3	7	5.5	3	2.3	2.40 (0.62-9.28)	
Years 4 and 5	6	4.0	3	2.0	2.05 (0.15-8.18)	

*RH indicates relative hazard; CI, confidence interval; and CHD, coronary heart disease.
†Event rates per 1000 women-years in the estrogen plus progestin or placebo group.
‡*P* values for tests of continuous trend in log-relative hazard.
§Primary CHD events include nonfatal myocardial infarction and CHD death.
¶Coronary revascularization includes coronary artery bypass graft surgery and percutaneous coronary revascularization.

The Heart and Estrogen/progestin Replacement Study (HERS)

The major findings:

In postmenopausal women with established coronary disease and an average age of 66.7 years, daily use of conjugated equine estrogens and medroxyprogesterone acetate did not reduce the overall risk for MI and CHD death or any other cardiovascular outcome during an average of 4.1 years of follow-up. This therapy did increase the risk of venous thromboembolic events and gallbladder disease.



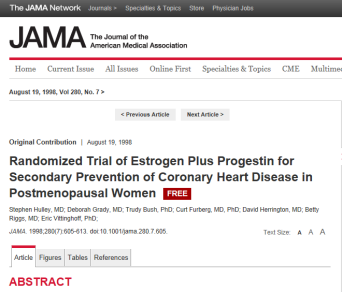
Background:

- Lipoprotein(a) [Lp(a)] has been found to be an independent risk factor for CHD events of men without known coronary artery disease.

- Few prospective studies have evaluated the importance of Lp(a) as a risk factor among women with CHD.

- Estrogen and the combination of estrogen and progestin lower Lp(a) levels in postmenopausal women.

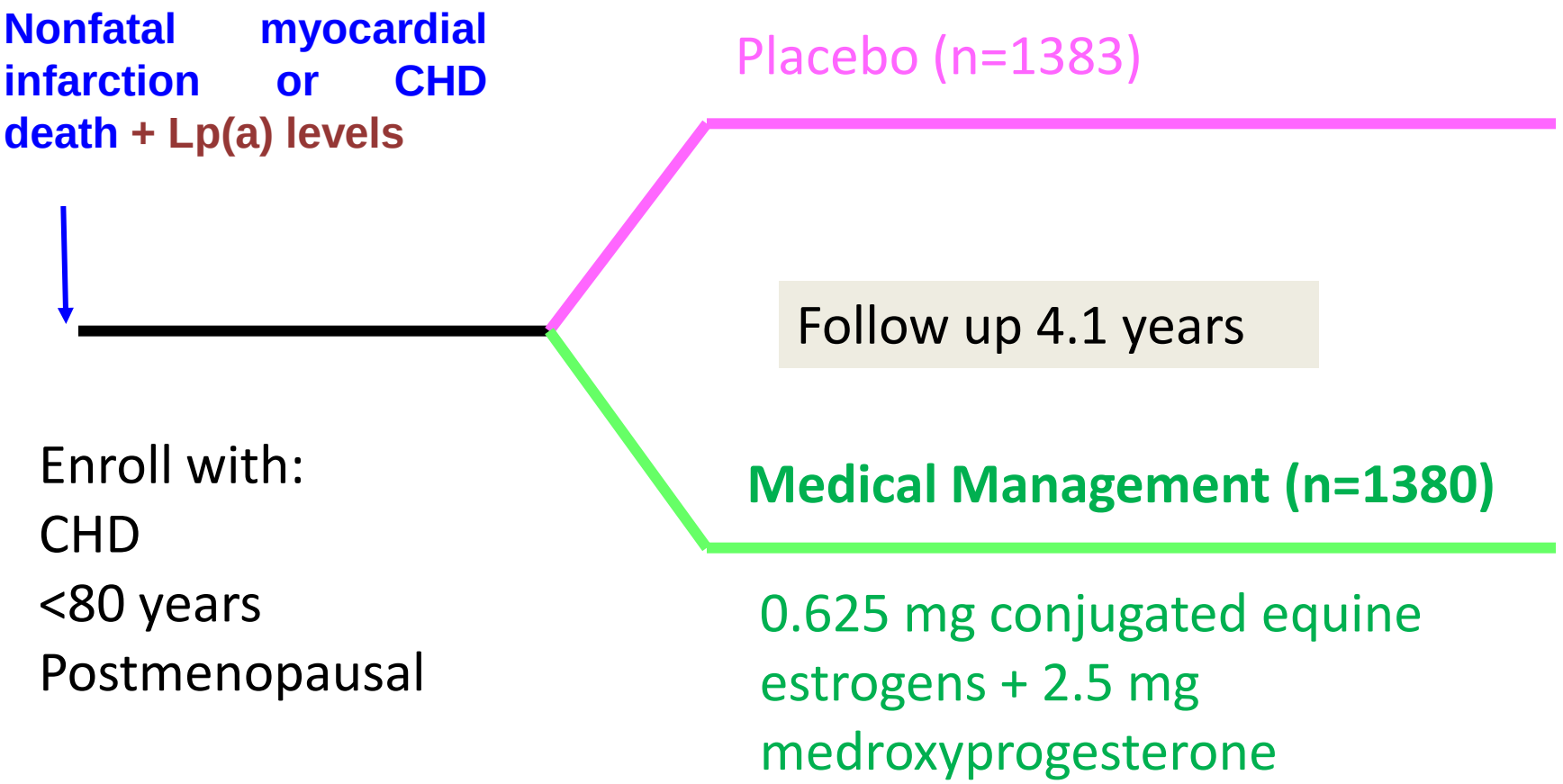
- Because these studies have been conducted in women without CHD and without assessment of CHD outcomes, the clinical importance of lowering Lp(a) levels among women is unknown.



The study question:

What are the relationships among treatment with estrogen and progestin, serum Lp(a) levels, and subsequent CHD events in postmenopausal women?

The Study Design



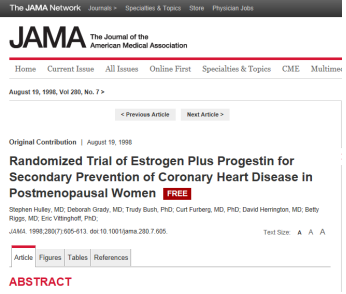


Table 2. Risk of Recurrent Coronary Heart Disease Events by Baseline Lipoprotein(a) Level Among Women Assigned to Placebo (n = 1383)*

	First Quartile (0.0-7.0 mg/dL) (n = 364)	Second Quartile (7.1-25.3 mg/dL) (n = 337)	Third Quartile (25.4-54.9 mg/dL) (n = 333)	Fourth Quartile (55.0-236.0 mg/dL) n = 348	*P* Value for Trend
Primary CHD events					
Events, No.	38	37	49	58	
Unadjusted HR (95% CI)	1.0	1.04 (0.7-1.6)	1.42 (0.9-2.2)	1.62 (1.1-2.4)	.008
Multivariate HR (95% CI)	1.0	1.01 (0.6-1.6)	1.31 (0.9-2.0)	1.54 (1.0-2.4)	.03
Myocardial infarction					
Event, No.	31	26	32	45	
Unadjusted HR (CI 95%)	1.0	0.90 (0.5-1.5)	1.14 (0.7-1.9)	1.55 (1.0-2.4)	.04
Multivariate HR (95% CI)	1.0	0.88 (0.5-1.5)	1.06 (0.6-1.8)	1.51 (0.9-2.5)	.08
CHD death					
Events, No.	10	12	21	16	
Unadjusted HR (95% CI)	1.0	1.27 (0.6-2.9)	2.31 (1.1-4.9)	1.64 (0.7-3.6)	.10
Multivariate HR (95% CI)	1.0	1.13 (0.5-2.7)	2.02 (0.9-4.4)	1.39 (0.6-3.2)	.25
CABG/PTCA					
Events, No.	64	56	57	82	
Unadjusted HR (95% CI)	1.0	0.93 (0.7-1.3)	0.99 (0.7-1.4)	1.41 (1.0-2.0)	.04
Multivariate HR (95% CI)	1.0	0.93 (0.7-1.3)	1.06 (0.7-1.5)	1.61 (1.1-2.3)	.006
Unstable angina					
Events, No.	29	31	25	35	
Unadjusted HR (95% CI)	1.0	1.16 (0.7-1.9)	0.96 (0.6-1.6)	1.28 (0.8-2.1)	.49
Multivariate HR (95% CI)	1.0	1.21 (0.7-2.0)	1.07 (0.6-1.8)	1.54 (0.9-2.6)	.17

*CHD indicates coronary heart disease; HR, hazard ratio; CI, confidence interval; CABG, coronary artery bypass graft surgery; and PTCA, percutaneous transluminal coronary angioplasty. Primary CHD events include nonfatal myocardial infarction and CHD death. Models are adjusted for other predictors ($P<.10$) including race/ethnicity, diabetes mellitus, waist-to-hip ratio, tobacco use, high- and low-density lipoprotein cholesterol levels, triglyceride level, and use of lipid-lowering agents, aspirin, and calcium channel blockers. To convert mg/dL to µmol/L, multiply by 0.0357. One subject was missing baseline lipoprotein(a) level and so was not included in the analysis.

Women in the highest Lp(a) quartile had a 54% (95% confidence interval [CI], 0%-140%) increased risk of primary CHD events compared with women in the lowest Lp(a) quartile.

ORIGINAL CONTRIBUTION

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Original Contribution | August 19, 1998

Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women FREE

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JAMA. 1998;280(7):605-613. doi:10.1001/jama.280.7.605

Text Size: A A A

Article Figures Tables References

ABSTRACT

Estrogen and Progestin, Lipoprotein(a), and the Risk of Recurrent Coronary Heart Disease Events After Menopause

Michael G. Shlipak, MD, MPH
Joel A. Simon, MD, MPH
Eric Vittinghoff, PhD
Feng Lin, MS
Elizabeth Barrett-Connor, MD
Robert H. Knopp, MD
Robert I. Levy, MD
Stephen B. Hulley, MD, MPH

Context Lipoprotein(a) [Lp(a)] has been identified as an independent risk factor for coronary heart disease (CHD) events. However, few data exist on the clinical importance of Lp(a) lowering for CHD prevention. Hormone therapy with estrogen has been found to lower Lp(a) levels in women.

Objective To determine the relationships among treatment with estrogen and progestin, serum Lp(a) levels, and subsequent CHD events in postmenopausal women.

Design and Setting The Heart and Estrogen/progestin Replacement Study (HERS), a randomized, blinded, placebo-controlled secondary prevention trial conducted from January 1993 through July 1998 with a mean follow-up of 4.1 years at 20 centers.

Participants A total of 2763 postmenopausal women younger than 80 years with coronary artery disease and an intact uterus. Mean age was 66.7 years.

Intervention Participants were randomly assigned to receive either conjugated equine estrogens, 0.625 mg, plus medroxyprogesterone acetate, 2.5 mg, in 1 tablet daily (n = 1380), or identical placebo (n = 1383).

Main Outcome Measures Lipoprotein(a) levels and CHD events (nonfatal myocardial infarction and CHD death).

LIPOPROTEIN(A) [LP(A)] HAS BEEN found to be an independent risk factor for coronary heart disease (CHD) events in most[1-7] but not all[8-10] prospective studies of men without known coronary artery disease. Few pro-

Lp(a) is an independent risk factor for recurrent CHD in postmenopausal women and that treatment with estrogen and progestin lowers Lp(a) levels.

Estrogen and progestin therapy appears to have a more favorable effect (relative to placebo) in women with high initial Lp(a) levels than in women with low levels.

Preparing for Precision Medicine

Reza Mirnezami, M.R.C.S., Jeremy Nicholson, Ph.D., and Ara Darzi, M.D.

Ms. H. is a 35-year-old woman from Japan who has had a cough for 3 weeks. Her physician sends her for an x-ray and CT scan that reveal an advanced lesion, which a biopsy confirms to be non–small-cell lung cancer. She has never smoked. Can anything be done for her?

Had Ms. H.'s cancer been diagnosed before 2004, her oncologist might have offered her a treatment to which about 10% of patients have a response, with the remainder gaining a negligible survival benefit and experiencing clinically significant side effects. But her diagnosis was made in 2011, when her biopsy tissue could be analyzed for a panel of genetic variants that can reliably predict whether the disease will respond to treatment. Her tumor was shown to be responsive to a specific targeted agent, whose administration led to a remission lasting almost a year; her only side effect was a rash.

This scenario illustrates the fundamental idea behind personalized medicine: coupling established clinical–pathological indexes with state-of-the-art molecular profiling to create diagnostic, prognostic, and therapeutic strategies precisely tailored to each patient's requirements — hence the term "pr
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Toward Precision Medicine:

Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease

Committee on A Framework for Developing a New Taxonomy of Disease

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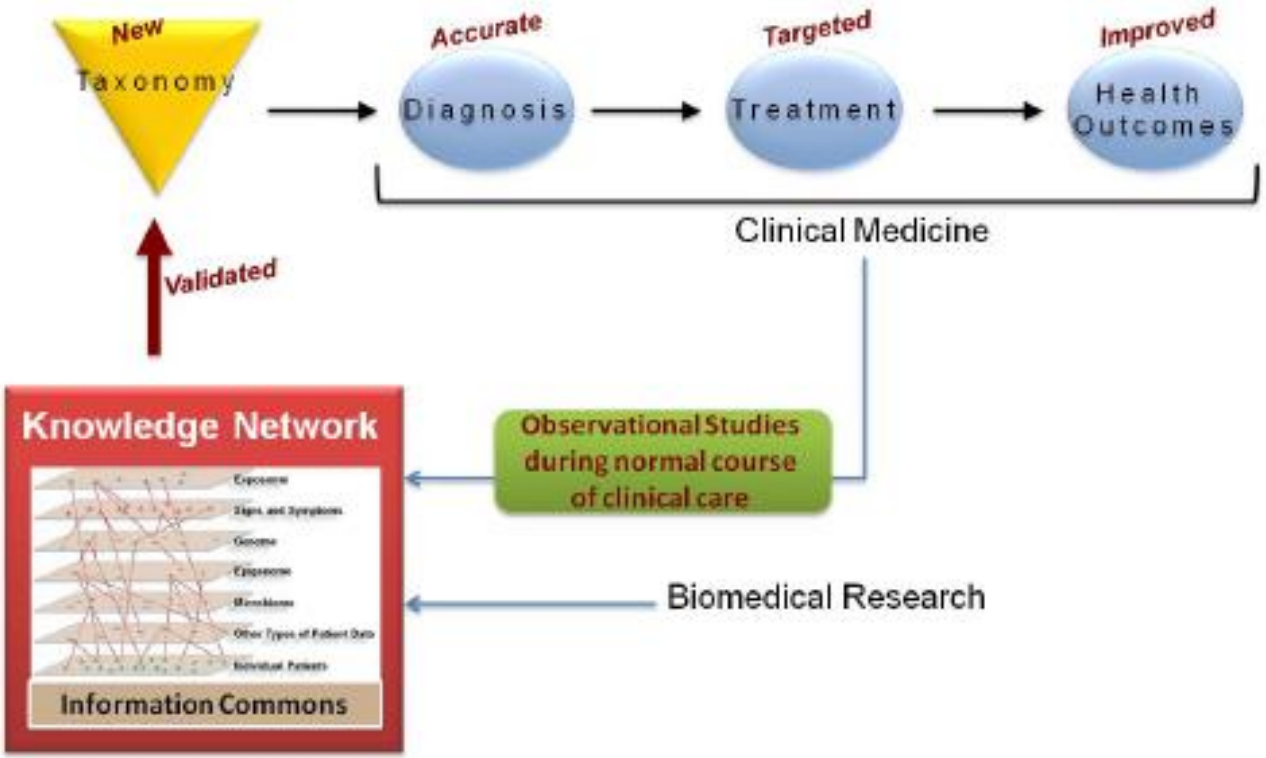


Figure S-1: Creation of a New Taxonomy first requires an "Information Commons" in which data on large populations of patients become broadly available for research use and a "Knowledge Network" that adds value to these data by highlighting their interconnectedness and integrating them with evolving knowledge of fundamental biological processes.

Components of an Original Research Paper

- Title
- Authors
- Abstract
- Keywords
- Introduction
- Materials and Methods
- Results
- Discussion
- Acknowledgement
- References

- What are your major findings?
- Answer all points raised in Materials and Methods.
- No new parameters.
- No mismatch in numbers between text and tables/figures.
- Follow a logical sequence based on the tables and figures presenting the findings to answer the question or hypothesis.

Presenting your results effectively

- Introduce each experimental section with a clear description of the experimental design and aims.
- Figures should have a brief description (a legend), providing the reader sufficient information to know how the data were produced.
- If the table or figure contains only one or two items, the information can be summarized instead.

Presenting your results effectively

Title-brief, informative &effective

Experimental design and aim

Major findings

Interpretation of your findings

All TSP Isoforms Induce Synapse Formation

There are five TSP isoforms in mammals, which fall into two groups according to their domain structure and oligomerization states (Figure 1A). Trimeric subgroup A TSPs, TSP1 and 2, are synaptogenic (Christopherson et al., 2005). **To determine whether pentameric subgroup B TSPs are also synaptogenic, we cultured RGCs in the presence of astrocytes or with TSP 1, 3, 4, or 5. All subgroup B TSPs increased synapse number significantly to similar levels as TSP1 or astrocytes (Figures 1B–1D). These results suggest** that the synaptogenic domain of TSP is located in the conserved C-terminal portion of TSP, which is common to all isoforms spanning the EGF-like repeats, the calcium-binding repeats, and C-terminal L-type lectin-like globular domain.

Presenting your results effectively

- **α2δ-1-Mediated Synapse Formation Does Not Depend on Calcium Channel Surface Level or Function**
- α2δ-1 is known to enhance calcium channel function and trafficking (Arikkath and Campbell, 2003). **We therefore investigated whether** the activity of α2δ-1 in synapse formation is linked to its role in increasing calcium currents or calcium channel levels. Gene expression analysis of RGCs show that these cells express predominantly postsynaptic L-type and presynaptic N- and P/Q-type voltage gated calcium channels (VGCCs). **To directly test whether** VGCC function was required for astrocyte-induced synapse formation, **we added** L-type calcium channel blockers to RGCs to block L-type channel function. **These drugs had no effect on SD2-induced synapse formation (Figure S5 A).**

- **Title**
- **Design/aim**
- Results
- **Design/aim**
- **Results**

Presenting your results effectively

- Similarly presynaptic N- and P/Q-type channel blockers did not block TSP-induced synapse formation (data not shown). **We next investigated** whether increase of postsynaptic L-type calcium channel expression in RGCs would enhance synapse formation. Overexpression of L-type α1C and β subunits in RGCs had no effect on astrocyte-induced synapse formation (Figure S5 B). **Finally, we tested whether** TSP treatment would lead to an increase in cytoplasmic calcium levels in RGCs. Neither acute nor long-term TSP treatment led to a noticeable rise in spontaneous calcium oscillations in RGCs (Figure S6). **Taken together, these results show that the role of α2δ-1 in synapse formation cannot be directly linked to calcium channel expression levels or function.**

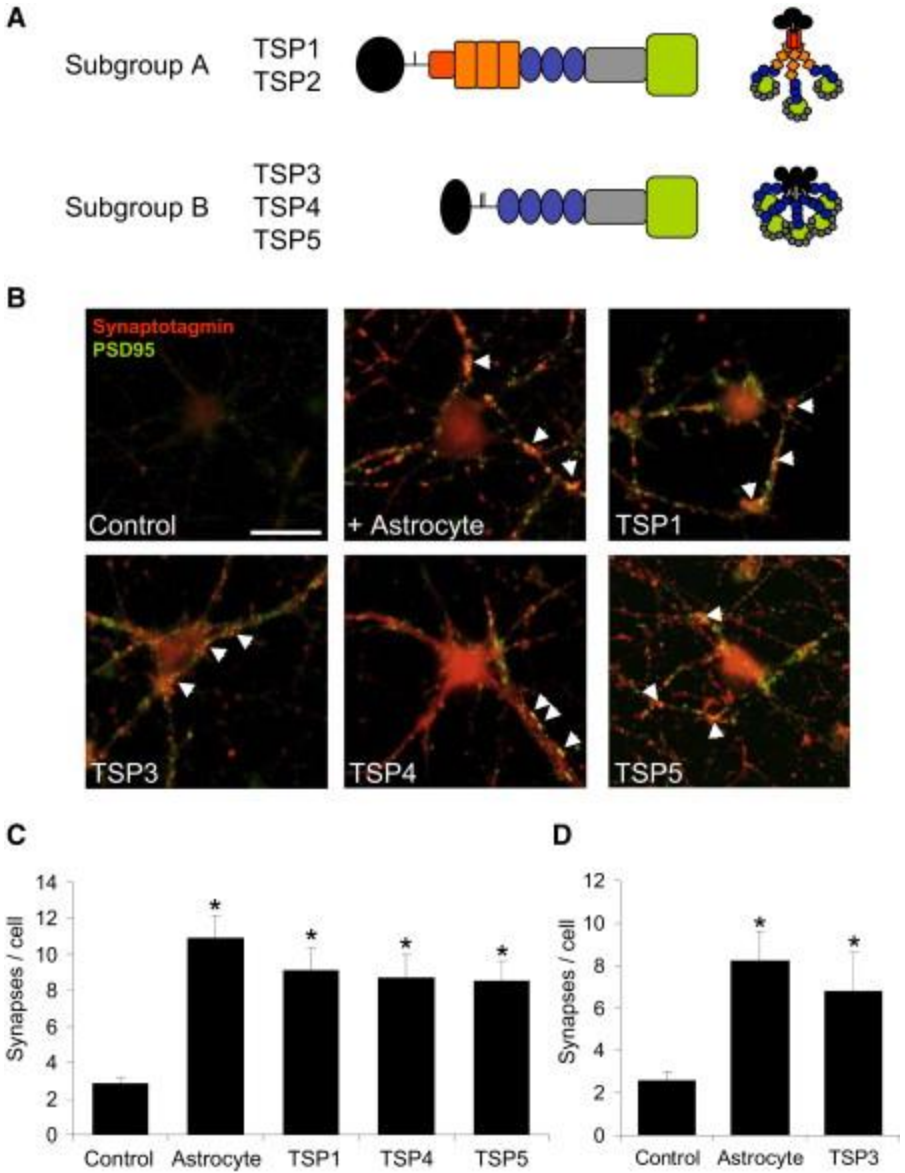
Presenting your results effectively

- Introduce each experimental section with a clear description of the experimental design and aims.
- Figures should have a brief description (a legend), providing the reader sufficient information to know how the data were produced.
- If the table or figure contains only one or two items, the information can be summarized instead.

- **Save your images in the highest resolution!!!**
- Show the figures to your colleagues and ask for their suggestions before you submit.

Presenting your results effectively

Figure 1 All Thrombospondin Isoforms Are Synaptogenic
(A) TSPs are divided into two subgroups. The N-terminal domain (black), the procollagen repeat (red), and properdin-like repeats (orange), EGF-like repeats (blue), calcium binding repeats (gray), and C-terminal L-lectin like globular domain (green) are shown.
(B) Immunostaining of RGCs for synaptotagmin (red) and PSD-95 (green). White arrows point to colocalized synaptic puncta. The scale bar represents 30 μm.
(C and D) Quantification of the effects of astrocytes, purified TSP1, 4, and 5 (8 nM each) (C) and conditioned media from COS7 cells overexpressing either TSP3 or empty vector (D) on synapse number. In all graphs, n = 20 cells. Error bars show the mean ± SEM, *p < 0.05.



Writing an effective discussion

- Title
- Authors
- Abstract
- Keywords
- Introduction
- Materials and Methods
- Results
- Discussion
- Acknowledgement
- References

- Recapitulate major findings .
- Discuss major findings in light of available data .
- Discuss important minor findings .
- Provide alternative explanations .
- What are the strengths and limitations of the study ?
- Implications of findings .

Writing an effective discussion

- Title
- Authors
- Abstract
- Keywords
- Introduction
- Materials and Methods
- Results
- Discussion
- Acknowledgement
- References

- Describe what your results mean in context of what was already known about the subject
- Indicate how the results relate to expectations and to previous findings by others
- Explain how the research has moved the body of scientific knowledge forward
- Do not extend your conclusions beyond what is directly supported by your results - avoid undue speculation
- Unanswered questions and future research .
- Summary / conclusion .

Writing an effective cover letter

- June 24, 2009
- Dear Editors,
- We would like to submit the enclosed manuscript entitled "High-altitude pulmonary edema (HAPE) in unacclimatized persons is associated with abnormal changes in the coagulation and fibrinolytic system" by Ren et al. for consideration as a Brief Report in JAMA. We report our investigation of changes in the fibrinolytic and coagulation system in a large cohort of patients with HAPE. Previous reports of HAPE only involve fewer than 10 subjects. We found that HAPE is associated with abnormalities in the fibrinolytic system and these abnormalities are associated with the severity of HAPE. Our findings provide further insight into an illness that becomes more common with increased leisure activities in high altitude.

- Introduce the editor to your manuscript

- Point out what type of publication you would like to have it published
- Provide the name of the journal.

- Tell what your investigation is about and be brief

and its significance.

Writing an effective discussion

- **Gabapentin Is a Powerful Blocker of Synapse Formation**
- Our findings suggest that GBP blocks TSP-induced synapse formation by interfering with TSP-α2δ-1 interaction. GBP binding to α2δ-1 involves a region just upstream of the VWF-A domain in α2 (Wang et al., 1999). Therefore, it is unlikely that TSP and GBP compete for the same binding site. It is known for integrins that conformational changes in VWF-A domains can be constrained by interactions made by regions flanking this domain (Bork and Rohde, 1991,Whittaker and Hynes, 2002). We propose that GBP binding to α2δ-1 restricts the conformation of the VWF-A domain and keeps α2δ-1 in its "inactive conformation." This perturbs the TSP-α2δ-1 interaction and inhibits activation of the synaptogenic signaling complex (Figure S13).

- Describe what your results mean in context of what was already known about the subject
- Related to work by others.
- Provide explanations

Writing an effective discussion

- GABA, leucine, and isoleucine can also bind to α2δ-1, albeit at lower affinity than GBP (Dooley et al., 2007), and thus they can be physiological ligands for α2δ-1 and regulate excitatory synapse formation. In agreement with this, we found that high concentrations of GABA inhibited synapse formation in culture. Such high concentrations of GABA are present in the CNS right next to a GABAergic axon. Dendritic filopodia in the developing brain actively seek for synaptic partners and establish exclusively glutamatergic contacts. Interestingly, dendritic filopodia that contact a GABAergic axon never stabilize the contact and retract (Lohmann and Bonhoeffer, 2008,Wierenga et al., 2008). In future studies, it will be interesting to explore whether α2δ-1 functions as a physiologically relevant GABA receptor that enables initial selectivity for the formation of excitatory synapses by dendritic filopodia.

- Indicate how the results relate to expectations and to the literature previously cited

- Unanswered questions and future research .

Writing an effective discussion

- **α2δ-1-TSP Interaction Regulates Synapse Formation during Development and after Injury**
- The ability of GBP to strongly decrease synapse formation in wild-type mouse brains points to a critical role for TSP-α2δ-1 interaction and astrocytes in driving synaptogenesis in vivo. In addition, the correct execution of barrel cortex plasticity depends on TSP-induced synapse formation. Since the unlesioned barrel cortices are formed normally both in GBP injected and *TSP1/2* KO mice, TSPs might specifically play a role in synaptic remodeling plasticity upon injury in this system. These findings add to the growing data that astrocytes not only actively contribute to normal synaptogenesis but also mediate synaptic remodeling events after injury.

- Recapitulate major findings

- Explain how the research has moved the body of scientific knowledge forward

Writing an effective discussion

- Since GBP strongly blocks TSP-induced synapse formation within its therapeutic concentration, it is possible that inhibition of excitatory synapse formation is an important mode of its therapeutic action in epilepsy and pain. Reactive astrocytosis is prominent both in epileptic lesions and in the spinal cord after peripheral nerve injury that leads to neuropathic pain (Liu et al., 2000,Ridet et al., 1997). Reactive astrocytes express high levels of TSP1 and 2 (Lin et al., 2003). Similarly, upon injury in the spinal nerve, both α2δ-1 and TSP4 genes are upregulated in the spinal cord (Valder et al., 2003,Wang et al., 2002). Increased α2δ-1 levels were shown to lead to enhanced excitatory synaptic transmission and elevated neuropathic pain states (Li et al., 2004,Li et al., 2006). Similarly, there is increased excitation in the epileptic brain (Prince, 1999). All these observations point to the possibility that aberrant excitatory synaptogenesis may contribute to the pathophysiology of neuropathic pain and epilepsy. Thus GBP may act by limiting these excess synapses from forming, a possibility which can now be directly tested in animal models of these diseases. **In conclusion, by identifying α2δ-1 as a receptor for TSP mediated glial-induced synapse formation, we have gained molecular understanding not only of astrocytes' role in synapse formation in health and disease, but also of the process of synapse formation itself.**

- **Provide a strong conclusion**

Components of an Original Research Paper

- Title
- Authors
- Abstract
- Keywords
- Introduction
- Materials and Methods
- Results
- Discussion
- Acknowledgement
- References

- How many?
- What are they?- anything that is not common knowledge or not originated from the research work should be credited with a citation.
- How to set them out (EndNote)?
- Avoid references that are difficult to find.

The order of writing an original research paper

- Figures and tables
- Methods, results and discussion
- Conclusions and introduction
- Abstract and title

Components of an Original Research Paper

- Title
- Authors
- Abstract
- Keywords
- **Introduction**
- **Materials and Methods**
- **Results**
- **Discussion**
- Acknowledgement
- References

- Make the paper as brief as possible.

Writing an effective cover letter

- June 24, 2009
- Dear Editors,
- We would like to submit the enclosed manuscript entitled "High-altitude pulmonary edema (HAPE) in unacclimatized persons is associated with abnormal changes in the coagulation and fibrinolytic system" by Ren et al. for consideration as a Brief Report in JAMA. We report our investigation of changes in the fibrinolytic and coagulation system in a large cohort of patients with HAPE. Previous reports of HAPE only involve fewer than 10 subjects. We found that HAPE is associated with abnormalities in the fibrinolytic system and these abnormalities are associated with the severity of HAPE. Our findings provide further insight into an illness that becomes more common with increased leisure activities in high altitude.

- Introduce the editor to your manuscript

- Point out what type of publication you would like to have it published
- Provide the name of the journal.

- Tell what your investigation is about and be brief

and its significance.

Writing an effective cover letter

- All of the authors have participated in or contributed to the study and have read and approved the manuscript submitted. No duplicate publication or submission of the manuscript has been made elsewhere. There will be no conflict of commercial interest for any of the authors with the publication of the manuscript. Subject to acceptance for publication in your journal, all of the authors have agreed for the transfer of copyright to the publisher of the said journal.
-
- Questions and future correspondence should be addressed to Dr. Ren at the address shown above.
-
- Thank you for your kind consideration of our manuscript.
-
- Sincerely yours,

Writing an effective cover letter

- Dear Editor:
-
- Please find enclosed a manuscript entitled "HDMX Regulates p53 Activity and Confers Chemoresistance to 3-Bis(2-Chloroethyl)-1-Nitrosourea," which we would like to submit for publication in *Neuro-Oncology*.
- All authors have reviewed and approved this manuscript. We know of no conflicts of interest for any authors regarding this manuscript. Neither the submitted paper any similar paper, in whole or in part, other than an abstract or preliminary communication, has been or will be submitted to or published in any other printed or digital publication.

- Introduce the manuscript
- Provide the name of the journal.
- No duplication and conflict of interest statement.

Writing an effective cover letter

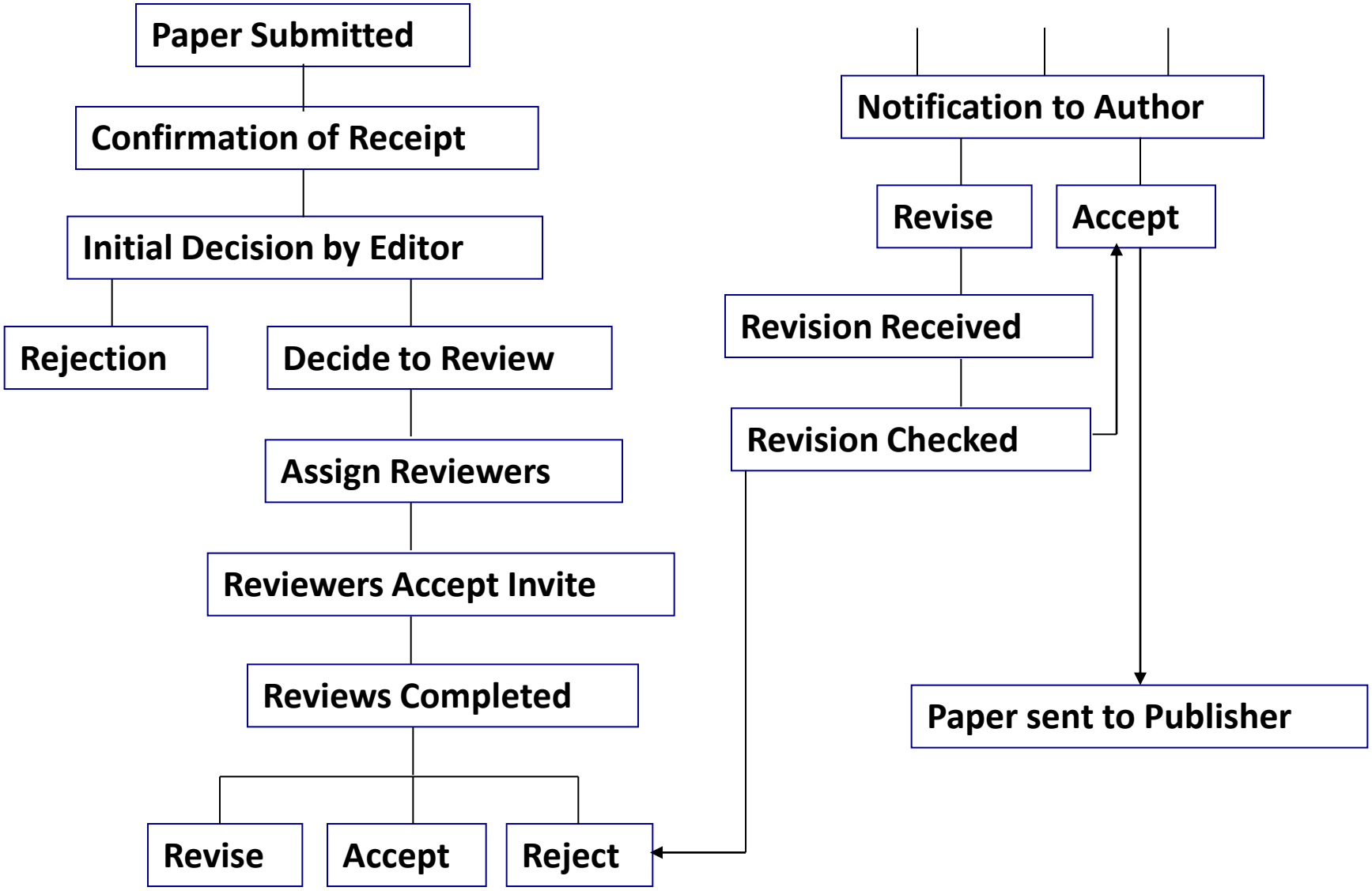
- We present the novel finding that HDMX confers GBM cells chemoresistance to 3-bis(2-Chloroethyl)-1-nitrosourea (BCNU), a chemotherapeutic agent in use for brain tumors and other solid tumors, by regulating p53 activity. Chr1q32 amplification has been identified in this study and others as a prominent genetic lesion for the carcinogenesis of glioblastoma. We further show by genetic screening that *HDMX* is the most commonly amplified and overexpressed gene in the minimal amplicon of chr1q32 and *HDMX* amplifications are mutually exclusive of *TP53* mutations and *MDM2* amplifications. We also demonstrate that HDMX stabilizes p53 to promote DNA repair and attenuates tumor response to BCNU. In summary, HDMX exhibits bona fide oncogenic properties and offers a promising molecular target for GBM therapeutic intervention.
- We are submitting the manuscript as a *Basic and Translational Investigations* report. The subject category is in Tumor Biology.
- Thank you for consideration of this manuscript.
- Sincerely,

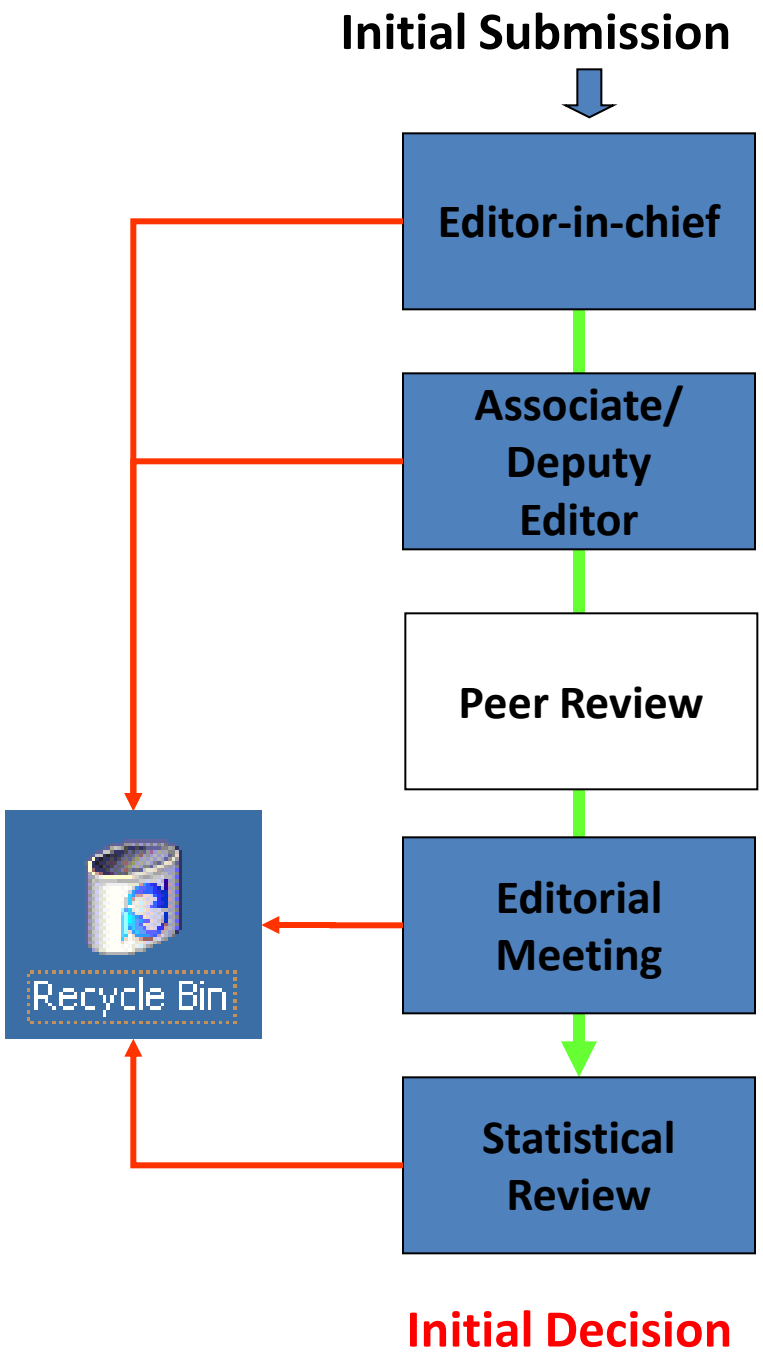
- Tell what your investigation is about and be brief

and its significance.

- Point out what type of publication you would like to have it published

Overview of Peer Review Process



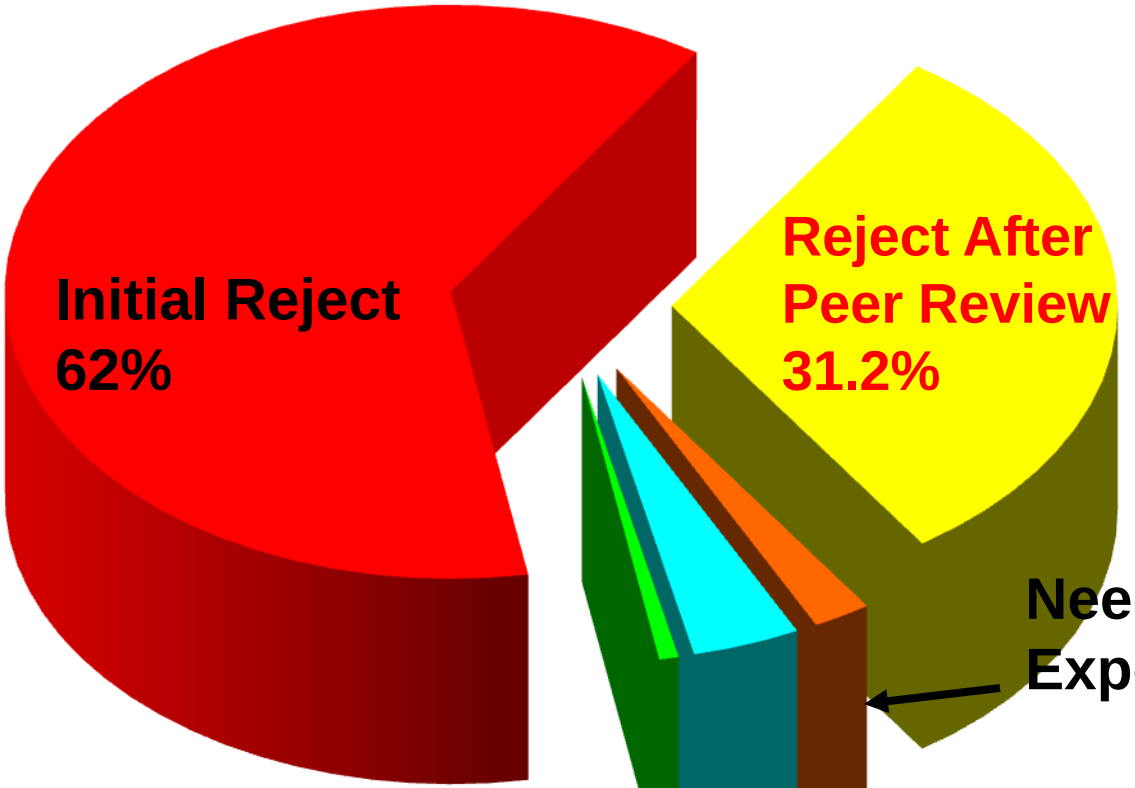


About 10% of papers are rejected at this stage. Assigned manuscripts are sent to the Associate Editors

Editorial process at NEJM
Courtesy of Dr. Drazen

Editorial process at NEJM
Courtesy of Dr. Drazen

Possible Decisions



Editors use the Reviews

- Once reviews are in the editor reads the paper and the reviews
- The editor, not the reviewer, makes the decision about the paper
- Reviewers' comments are valuable, but reviewers are only consultants to the thinking process

Editorial process at NEJM
Courtesy of Dr. Drazen

How to respond to critiques

- The reviewer determines if your manuscript is suitable for publication in the journal to which it is submitted.

- Novelty
- Significance
- Relevance
- Quality and novelty of the experimental design
- Data interpretation
- Style and presentation of the data.

How to respond to critiques

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The Top 10 Reasons Why Manuscripts Are Not Published

10. Picking the wrong journal
9. Submitting a manuscript in a format that does not match what the journal publishes
8. Not following the manuscript preparation instructions
7. Poor writing
6. Getting carried away in the discussion
5. Suboptimal reporting of the results
4. Inadequate description of the methods
3. Poor study design
2. **Failure to revise and resubmit following peer review**
1.Failure to write and submit a full manuscript after presenting the abstract.

Respiratory Care (2004) 40:1246

How to respond to critiques

- Your letter to the editor should start politely.
- Response letters should state that the author thanks the reviewers for their time and effort and their contributions to the work.
- Address the comments of the reviewers and/or conduct the recommended experiments to strengthen the work.
- The goal is to move the work forward and figure out how to satisfy the reviewer.

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- Response letters should state that the author thanks the reviewers for their time and effort and their contributions to the work.
- Address the comments of the reviewers and/or conduct the recommended experiments strengthened the work.

- The goal is to move the work forward and figure out how to satisfy the reviewer.

How to respond to critiques

- Provide a point by point response to each reviewer's concerns.
- If your response is supported by the literature, quoting papers and supplying references will strengthen your point.
- In places where you and the reviewer agree, you should note in the manuscript where you have made revisions reflecting the reviewer's concerns. This will help the editor and the reviewer (if the manuscript is sent out for re-review) locate your changes and determine if you have really addressed the issues.

How to respond to critiques

Dear Dr. Du

: Your manuscript entitled, "Treatment of Femoral Head Loss Secondary Septic Arthritis in Infancy With Modification of Albee's Arthroplasty," number JBJS-D-09-00201, has been reviewed by two experienced pediatric orthopaedic surgeons, as well as by myself. The comments of these clinical reviewers are included below. In addition, your manuscript was reviewed by one of the methodology and statistics editors for JBJS and the comments of that editor are also below.

Based on the reviews, the decision has been made to not accept your manuscript for publication in JBJS. I know this is not the decision you desired, but I hope that the comments of the three reviewers will be of help to you as you revise your manuscript for submission to another orthopaedic journal. Thank you for submitting your research report to JBJS for our consideration.

In accordance with our Copyright Transfer and Author Agreement, The Journal hereby re-conveys to the authors, without any representation, warranty or recourse, all of the rights (including copyrights) in the Work that were assigned to The Journal by the authors under that Agreement and are now held by The Journal.

Sincerely,

Vernon T. Tolo, MD
Deputy Editor

How to respond to critiques

- August 23, 2009
- Dear Dr. Vernon T. Tolo,
- Thank you for your having our manuscript (JBJS-D-09-00201) entitled “Treatment of Femoral Head Loss Secondary Septic Arthritis in Infancy with Modification of Albee's Arthroplasty” reviewed. We regret to learn the decision by JBJS not to accept our manuscript. However, we are very encouraged by the positive comments by the reviewers who have pointed out problems and deficiencies with the manuscript, but most of all they recognize the value of our work, the publication of which will be of great help to our fellow pediatric orthopedic surgeons in managing the severe sequelae of septic arthritis of the hip in young children.

- Start politely and thanks the editor for sending the manuscript for review.
- Be positive and emphasize the value/significance of your work.

How to respond to critiques

- We have revised the manuscript in accordance with the suggestions by the reviewers. In it, we have addressed almost all of the concerns by the reviewers and have incorporated answers to their questions in the revised manuscript. In addition, we have enlisted the help of Dr. Bo Cui at the Department of Surgery, Duke University Medical Center, Durham, NC, USA in the final revision of the manuscript. We have also sought the advice for statistical analysis from Dr. Xiutang Cao, a statistician at the Fourth Military Medical University China. We would like to ask your kind reconsideration of the manuscript either as a new manuscript or as a revised manuscript and we would also like to have the same reviewers review the manuscript if possible. Though septic arthritis of the hip in young children is uncommon, it is often devastating to those who have the disease. Our experience and the results of our retrospective study of modified Albee's arthroplasty in young patients with the severe sequelae of septic arthritis of the hip will be useful for pediatric orthopedic surgeons all over the world who face this problem rarely.

- Address comments/concerns by the reviewers.
- Be specific about your request.
- Emphasize the value of your work

How to respond to critiques

- Again all the authors have read the final manuscript and agreed to its publication if accepted by the journal. No duplicate publication or submission of the manuscript has been made elsewhere.
- We have detailed our responses to the reviewers and also documented the changes in the responses that are appended at the end of this letter.
- If you or the reviewers have any questions, please do not hesitate to contact me.
- Thank you for your consideration of our manuscript.

- Indicate that you have made appropriate changes in the manuscript.

A commentary by Paul D. Sponseller, MD, is available at www.jbjs.org/commentary and as supplemental material to the online version of this article.

Evaluation of the Modified Albee Arthroplasty for Femoral Head Loss Secondary to Septic Arthritis in Young Children

By Xue-dong Li, MD, PhD, Bin Chen, MD, Jun Fan, MD, PhD, Chuang-yi Zheng, MD, Dong-xin Liu, MD, PhD, Hu Wang, MD, PhD, Xue Xia, MD, Shi-jun Ji, MD, and Shi-xin Du, MD, PhD

Investigation performed at the 1st Affiliated Hospital, Medical College of Shantou University, Shantou, Guangdong, China

Background: Surgical treatment options for femoral head deficiency in infants secondary to septic arthritis of the hip are varied and associated with uncertain long-term outcomes. The modified Albee arthroplasty has been considered an acceptable procedure; however, the long-term outcomes of this procedure have not been reported, to our knowledge. We evaluated the long-term outcomes of the modified Albee arthroplasty in young patients with severe sequelae of septic arthritis of the hip.

Methods: We retrospectively studied twenty-one children (twenty-one hips) in whom Choi type-IVB sequelae of septic arthritis of the hip had been treated with a modified Albee arthroplasty and six patients with the same sequelae who had been managed with simple observation. The Trendelenburg sign, pain, the range of motion, hip function, the Harris hip score, and limb-length discrepancy were assessed clinically. Remodeling of the femoral head, hip stability, and arthritic changes in the hip were evaluated radiographically.

Commentary & Perspective on "Evaluation of the Modified Albee Arthroplasty for Femoral Head Loss Secondary to Septic Arthritis in Young Children" by Xue-dong Li, MD, PhD, et al.

By Paul D. Sponseller, MD,*
Johns Hopkins Medical Institutions, Baltimore Maryland

THE JOURNAL OF BONE & JOINT SURGERY
JB&JS
This is an enhanced PDF from The Journal of Bone and Joint Surgery
The PDF of the article you requested follows this cover page.

In this month's issue of JBJS, Li et al. report the largest series of post-sepsis Choi type-IVB hip deformities that have been treated with this method. This series should be considered in the context of other reports on the same procedure. Why report on this "old" procedure now? The answer is because the solution seems still valid and this series is the largest one (twenty-one hips) and has the longest follow-up (minimum, three years; mean, ten years) with the most information on outcomes. The sample size and the follow-up are significant. Finally, this report can provide useful guidance to pediatric orthopaedic surgeons all over the world who treat this condition.

Commentary & Perspective By Paul D. Sponseller, MD*, Johns Hopkins Medical Institutions, Baltimore Maryland on:

"Evaluation of the Modified Albee Arthroplasty for Femoral Head Loss Secondary to Septic Arthritis in Young Children" by Xue-dong Li, MD, PhD, et al.

The article is also useful in part because it contains a detailed description of the procedure. This instruction, in combination with the decade-long follow-up of this uncommon problem, provides valuable information to guide us. The series of three line drawings illustrating the procedure is practical and ***helps make this a landmark paper.***

The Journal of Bone & Joint Surgery
JB&JS
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The PDF of the article you requested follows this cover page.

Evaluation of the Modified Albee Arthroplasty for Femoral Head Loss Secondary to Septic Arthritis in Young Children

Surgical Technique

By Xue-dong Li, MD, PhD, Bin Chen, MD, Shao-wei Luo, MD, Shi-jun Ji, MD, and Shi-xin Du, MD, PhD

Investigation performed at the 1st Affiliated Hospital, Medical College of Shantou University, Shantou, Guangdong, China

The original scientific article in which the surgical technique was presented was published in JBJS Vol. 92-A, pp. 1370-80, June 2010

ABSTRACT FROM THE ORIGINAL ARTICLE

BACKGROUND: Surgical treatment options for femoral head deficiency in infants secondary to septic arthritis of the hip are varied and associated with uncertain long-term outcomes. The modified Albee arthroplasty has been considered an acceptable procedure; however, the long-term outcomes of this procedure have not been reported, to our knowledge. We evaluated the long-term outcomes of the modified Albee arthroplasty in young patients with severe sequelae of septic arthritis of the hip.


The
Bitter
End

Frisch weht der Wind
Der Heimat zu.
Mein Irisch Kind,
Wo weilest du?
'You gave me hyacinths first a year ago;
They called me the hyacinth girl.'
-Yet when we came back, late, from the Hyacinth garden,
Your arms full, and your hair wet, I could not
Speak, and my eyes failed, I was neither
Living nor dead, and I knew nothing,
Looking into the heart of light, the silence.
Od' und leer das Meer.

T.S. Eliot, the Wasteland