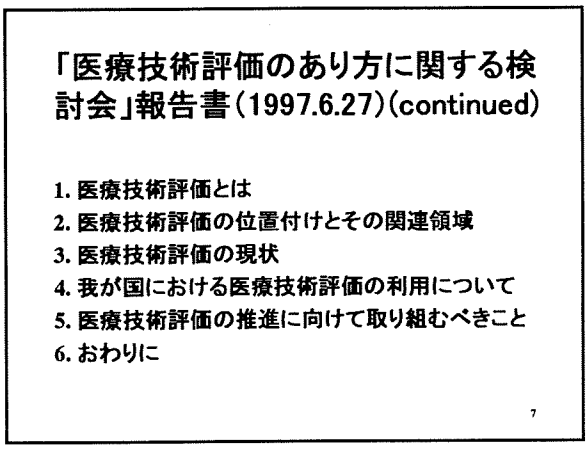
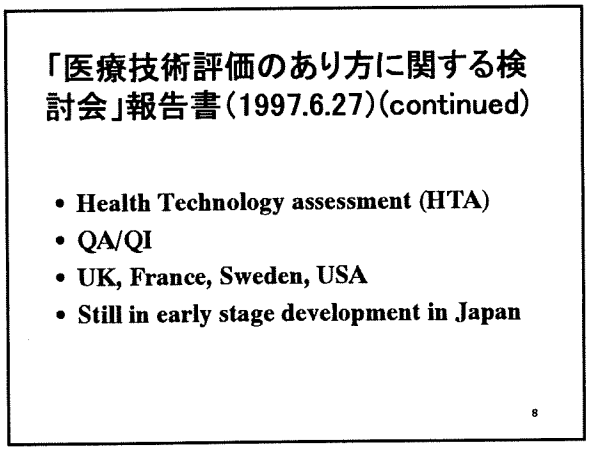
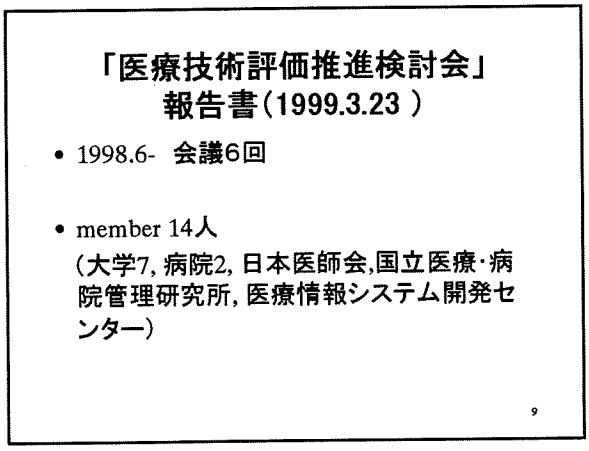


Slide 7-8 Contents of the 1997 HTA

This is a list of topics discussed in the report, which contains a comprehensive discussion of HTA. Quality assurance (QA) and quality improvement (QI) in health management, or "Kaizen" in Japanese, are also analyzed. It includes a survey of the status of HTA in other countries, such as France, Sweden, the United Kingdom, and the United States of America. The report reveals that HTA is in its early stage of development in Japan and should thus be further developed.





Slide 9 The second HTA report in March 1999

This is the second HTA report. The composition of the second group is basically the same as the first. The group, which also held six meetings, was made up of 7 members from academia, 2 from the hospitals, and one each from JMA, NIHSM, and the Medical Information System Development Center (MEDIS-DC), whose members are experts in medical informatics. Four members were the same as those who prepared the first report.

Slide 10-11 Contents of the 1999 HTA report

This second report is more focused on EBM. It mentions about randomized controlled trial (RCT) and meta-analysis. It is interesting to note that only in the second report did the term "randomized controlled trial" appear. It seems that the concept of randomization was not well recognized even by the very senior health officials or academicians in Japan. Now they seem to understand the concept better, and have discussed it. Meta-analysis

「医療技術評価推進検討会」
報告書(1999.3.23)(continued)

1. はじめに
2. 医療技術評価とEBMについて
3. EBMについて
4. 医療技術評価とEBMの総合的推進について
5. EBM推進のための環境整備について
6. 国民の臨床研究への理解と協力について
7. おわりに

10

「医療技術評価推進検討会」
報告書(1999.3.23)(continued)

- RCT, MA
- AHCPR, National Guideline Clearinghouse
- Center for Review and Dissemination (CRD)
- The Cochrane Collaboration
- Evidence-based clinical practice guidelines
  topics: priority setting
- Understanding from the public

11

EBMの推進に関する研究(1)

FY1999(平成11年度)　　FY2000(平成12年度)

医療技術評価総合研究事業

Clinical practice guidelines

Infrastructure development

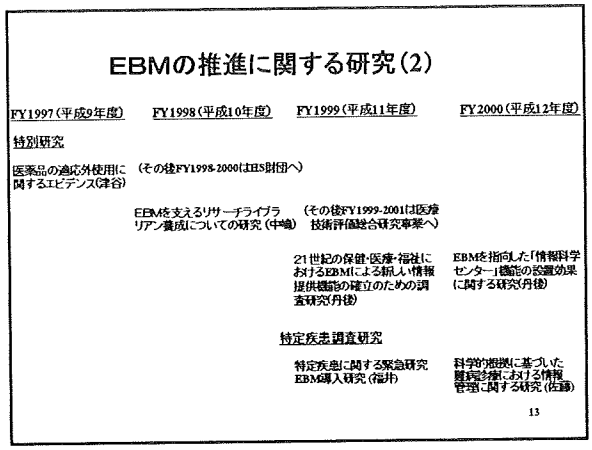
12

was briefly mentioned, as well as AHCPR National Guidelines Clearinghouse in the United States and the Center for Review and Dissemination (CRD) in U.K. I was actually invited to give a talk on the activities of the Cochrane Collaboration.

The report concludes that there should be evidence-based clinical practice guidelines. Hence a priority list of topics that focused on evidence-based clinical practice guidelines was developed. Another conclusion arrived at was that more understanding on clinical research, including clinical trials, is needed, because only by the participation of the patients/public in clinical research can strong evidence be generated. It has had a negative image before. So in order to improve clinical research, this group decided that there should be more advocacy and educational activities to the public. However, some items seems missing in the project. For instance, the registration of clinical trials sponsored by either government or the pharmaceutical industry, which is mainly aim to reduce publication bias and may contribute to improve the image of clinical trials is not well recognized in Japan.

Slide 12　The EBM project begins

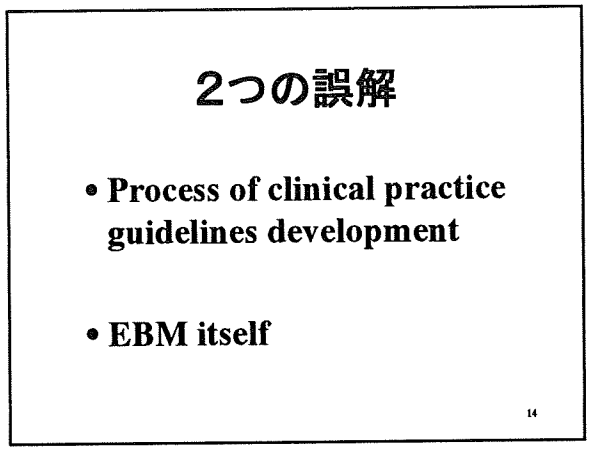
During the fiscal year 1999, the actual project sponsored by MHW, under the category of HTA, started with the development of the five guidelines. Each guideline cost JYE 30,000,000 or around US$ 300,000 for two years. The total budget for the fiscal year 1999 was JYE 80,000,000 or nearly US$ 1 million, including an information infrastructure project for training program development for a research librarian supporting EBM. For the fiscal year 2000, about US$ 4 million has been spent, with additional seven guidelines being developed and additional information infrastructure projects initiated or continuing. These projects include: the electronic search and hand search project; a training program and preparation of a syllabus for physicians; classification of nursing; development of an EBM support system which main activities is translation of "Clinical Evidence" into Japanese; an EBM database development; and, finally, one on alternative medicine. So now there are 8 ongoing projects.



Slide 13 EBM projects under other programs

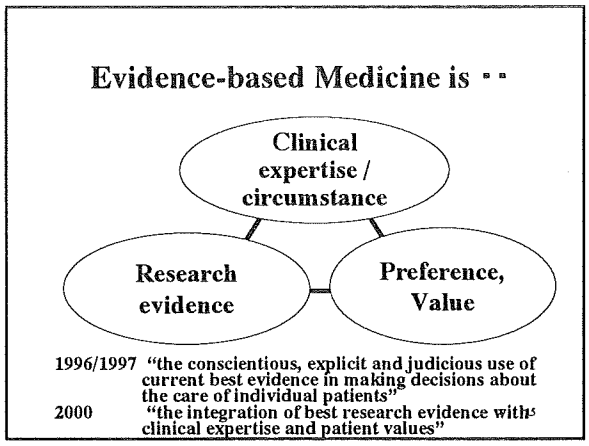
Aside from these there have been several projects on EBM under the category of "special research" sponsored by the MHW. The first one was Evidence for Off-Label Use of Drugs, for which I was the principal investigator in FY 1997. This was actually continued by another agency, the Japan Health Sciences Foundation, a quasi-government agency, for three years FY1998-2000. The training program development for the EBM research librarian project was originally under the category of special research in FY1998.

And in FY1999 there was a project hosted by the National Institute of Public Health (NIPH) under Dr. Toshiro Tango. This project is for the new information retrieval system in the 21st century. This was succeeded by a project on research the impact of development of information science center based on EBM. Actually, this project resulted from the idea of setting up an EBM information center using a model of the Cochrane Center. This is under the category of specialized disease examination study. In FY 1999 there was another project on how to introduce the EBM concept in special or intractable diseases or diseases which are very difficult to treat. There is also a continuating project on information management in this area in FY2000.



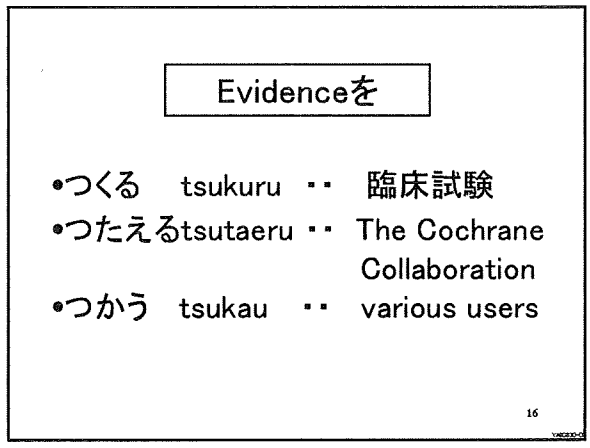
Slide 14 EBM vs. Clinical Practice Guidelines

There are altogether more than 20 EBM projects under the HTA program and others. The development of EBM has seemed to be going on smoothly in Japan. The reality, however, is different. There are actually two misunderstandings currently going on. There is the misunderstanding on the process of clinical practice guideline development. Some people consider such guidelines very restrictive in that they aim to control physicians' behavior. It is felt that the guidelines are biased towards reducing health costs in Japan. The other misunderstanding is on EBM itself.



Slide 15 Three component in EBM

I first clarify the misunderstanding of EBM. This is from the second version of David Sackett's textbook on EBM in 2000. EBM does not consist only by evidence. It is an integration of best-researched evidence with clinical experience and patient values.

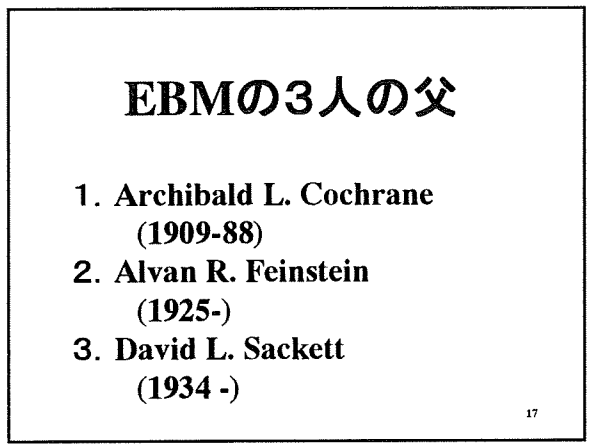


Slide 16 Three phase of evidence

There are three phase of evidence;
First is *tsukuru*, generation evidence through valid clinical trial.

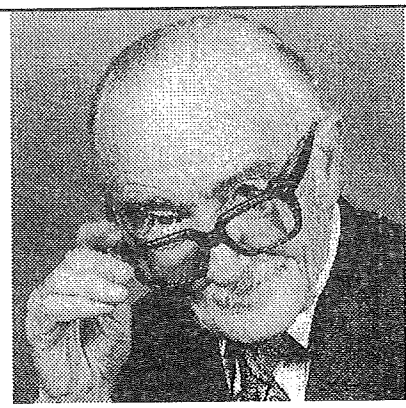
Second is *tsutaeru*, evidence are searched, appraised, synthesized and disseminated.

Third is *tsukau*, physicians, government officials, consumers and others use it



Slide 17 The fathers of EBM

It is said that there are three fathers of EBM development: Archie Cochrane, Alvan Feinstein, and David Sackett.



(Archibald Cochrane, 1909-1988)

18

Slide 18 Archie Cochrane

This is Archie Cochrane. He said three things.

Cochrane の言った3つの事

1. **All effective treatment must be free.**
2. **RCTの重要性**
3. **'Systematic Review'の重要性**
   - **(1) すべてのRCTから**
   - **(2) よいものだけを**
   - **(3) まとめて**
   - **(4) 遅れなく**
   - **(5) 必要な人に届ける**

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Slide 19 Cochrane's theses

One is that all effective treatment must be free. During its developmental stage in the United Kingdom, the National Health Service (NHS) had for its political slogan -- "All treatment must be free". Cochrane, however, had a different view. He said that "All **effective** treatment must be free".

So how can we find out if a treatment is effective? His answer to this was the randomized controlled trial. This is the second point.

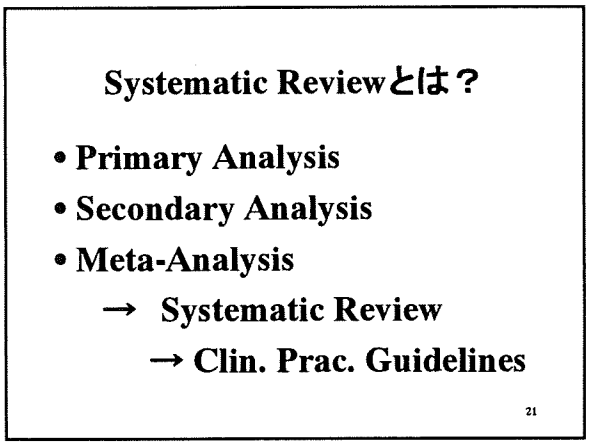
He also said that all clinical trials should be critically reviewed and appraised, results synthesized then, without delay, these results should be disseminated to persons in need of the information. This process is now called the 'systematic review'.

Systematic Reviewの7steps

研究テーマの設定
↓
研究結果を漏れなく収集
↓
各研究の妥当性の評価
↓
アブストラクトフォームに要約
↓
メタアナリシスによる統計学的解析
↓
結果の解釈
↓
編集と定期的更新

Slide 20 Seven steps of Systematic review

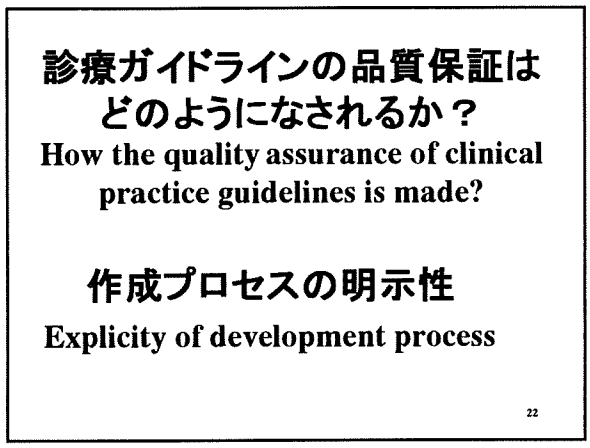
The method of systematic review consists of seven steps as follows: (1) Formulating the question; (2) Locating and selecting studies; (3) Assessing the validity of the study; (4) Collecting data; (5) Analyzing and presenting the results; (6) Interpreting the results; and (7) Editorial process and updating the review.



Slide 21 From primary analysis to meta-analysis

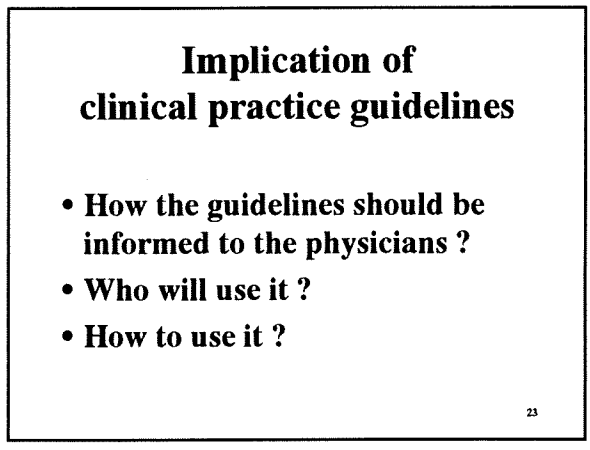
A synonym of "systematic review" is meta-analysis, although in the Cochrane Collaboration the word "meta-analysis" is confined to the mathematical method in synthesizing.

If you develop a protocol, execute a trial and analyze the result, you have what is called "primary analysis". The same data set may be analyzed by anyone else, which is then called secondary analysis. If there are more than two studies on the same research question, meta-analysis is used. And this is now called systematic review, which can thus be divided into: (1) systematic search, and (2) synthesis. The first part is very similar to the one used in clinical practice guideline development.



Slide 22 Quality assurance of clinical practice guidelines

How can quality assurance of clinical practice guidelines be made possible? Quality can be only be maintained through transparency in the development process. If there is a clear description of the whole process, then people will understand these guidelines better.

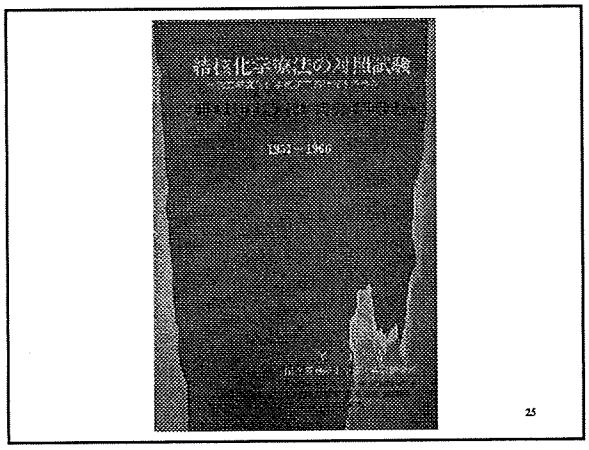


Slide 23 Implications of clinical practice guidelines

Now we also have to consider the implications—how the guidelines should be disseminated to physicians and others who may benefit from them and how they can be used. The answer is already mentioned in my explanation on EBM. Evidence in the form of clinical practice guidelines should be used in the integration of clinical circumstances and patient value.

Slide 24 Fifty years of randomized controlled trials

During the last three days, Dr. Joseph Lau from Boston and Dr. Liu Ming from Chengdu , China, conducted a systematic review workshop and during his lecture, Dr. Lau introduced some historical developments in randomized controlled trials using pictures. It was in 1948, when the first randomized controlled trial was published in the 30 October issue of *British Medical Journal*. It was a trial using streptomycin on pulmonary tuberculosis patients, a project headed by Dr. Austin Bradford Hill. This is a photo of some of the participants at the 50-year anniversary symposium of RCT held in London in 1998. Two of them are British, the rest Japanese. The person on second right in the back row is Dr. Iain Chalmers, Director of the U.K. Cochrane Center and developed the idea of the Cochrane Collaboration. Actually Dr. Archie Cochrane was his teacher. The next person is Dr. Richard Peto, a well-known biostatistician from Oxford



Slide 25 First randomized controlled trial in Japan

This is the report of first randomized controlled trial conducted by a Japanese in Japan - a RCT in the chemotherapy of tuberculosis. It was conducted in 1957-58 and published in 1960. This trial involved 114 national tuberculosis hospitals. But before this trial, there had been a trial conducted in Japan, although not by a Japanese.

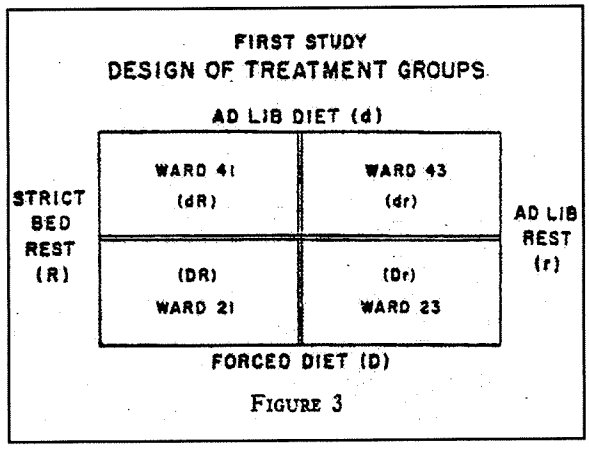
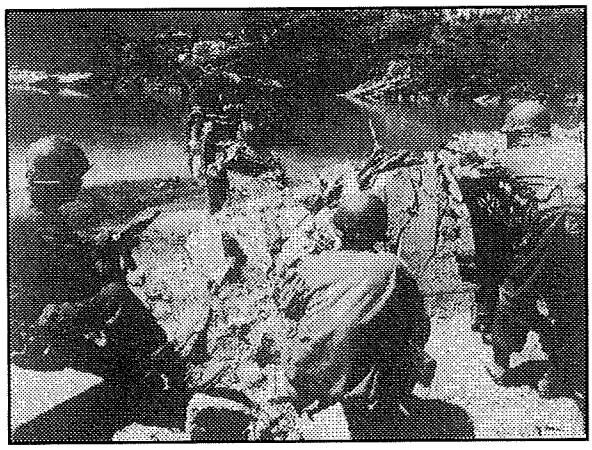


FIGURE 3

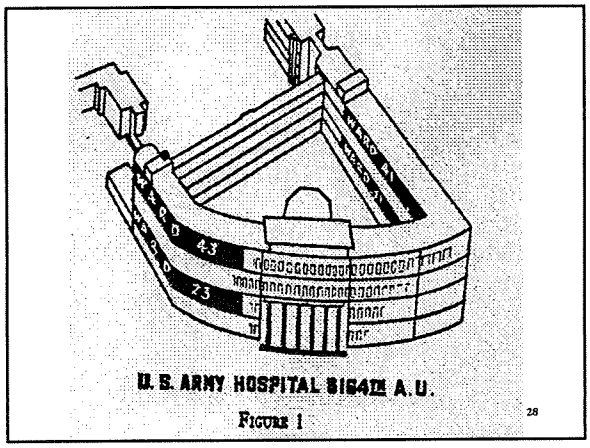
Slide 26 Two factorial designs

It was conducted by Dr. Thomas Chalmers, an American researcher. This study used two-by-two factorial designs - one prescribed strict bed rest vs ad lib rest, and the other, forced diet vs ad lib diet. The patients were randomly assigned to four wards.



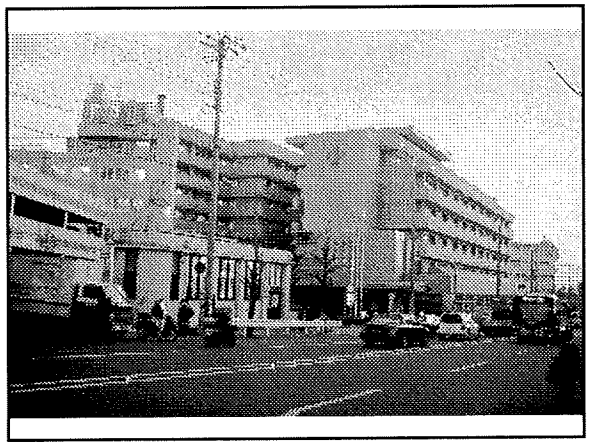
Slide 27 Soldiers in the Korean War

All the patients who participated in the trial were American soldiers who were infected with acute hepatitis during the Korean War of 1950-1951.



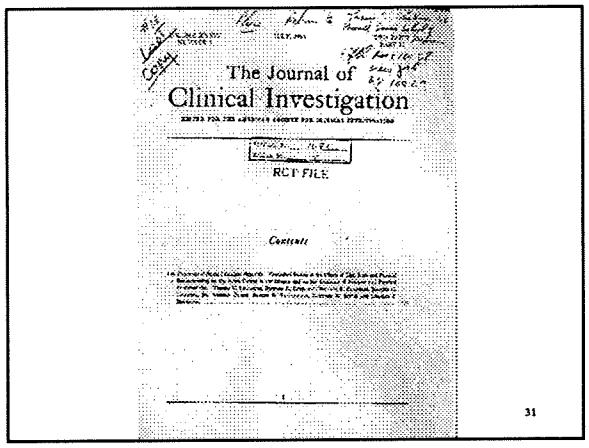
Slides 28 The US Army Hospital

The trial was conducted at the former Kyoto Red Cross Hospital, which was occupied by the Americans during the Korean War and later renamed the US Army Hepatitis Center. This figure in the trial paper in 1955 shows how the random assignments were made in the four different wards. Wards 21 and 23 on the second floor and Wards 41 and 43 on the fourth floor were used for this trial—the first ever randomized trial conducted in Japan. Unfortunately it was planned, conducted, and analyzed by Americans only. There was no Japanese involvement.



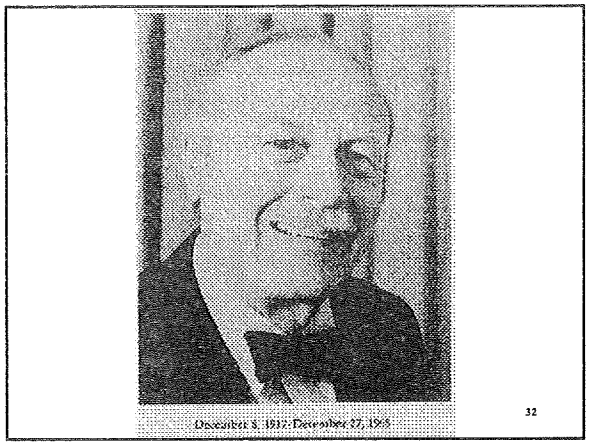
Slides 29-30 The Kyoto International Red Cross Hospital

This is the picture taken in 1991 by my friend in Osaka, which is close to Kyoto. You can see the same curved wall of the building, which was shown in the figure. Last February I visited the hospital when I gave a lecture at the Kyoto University, but I found that the building had been renovated and the impressive curved wall had disappeared.



Slide 31 The Journal of Clinical Investigation

This is the journal in which this study was published.



Slide 32 Dr. Thomas Chalmers

This is a picture of Dr. Thomas Chalmers, of the Technology Assessment Group at the Harvard School of Public Health. Actually he told me about the existence of this trial of 1951 and gave me a copy of the paper when I was in Boston in 1990.

高木兼寛の脚気trial

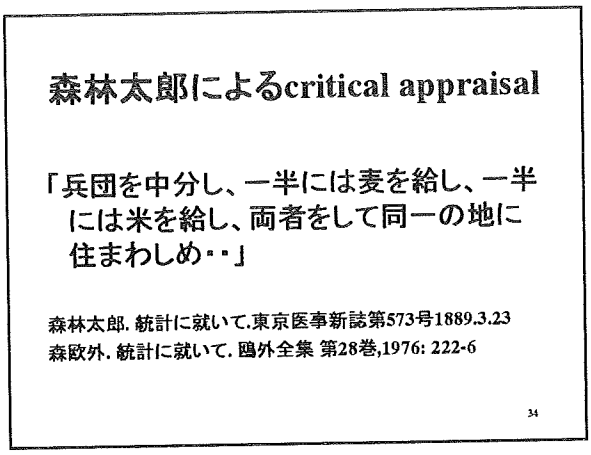
		Beriberi		
	+	(death)	-	total
龍驤(1882.12.19-83.10.15 NZ, Chile, Peru, Hawaii)	169	(25)	207	376
筑波(1884.2.2-11.16) NZ, Chile x2, Hawaii)	16	(0)	319	333

reference: Takagi B. *Lancet* 1906; May26: 1451-5
山下政三. 明治期における脚気の歴史. 東大出版会, 1988[33]

Slide 33 Study on beriberi by Dr. Takagi

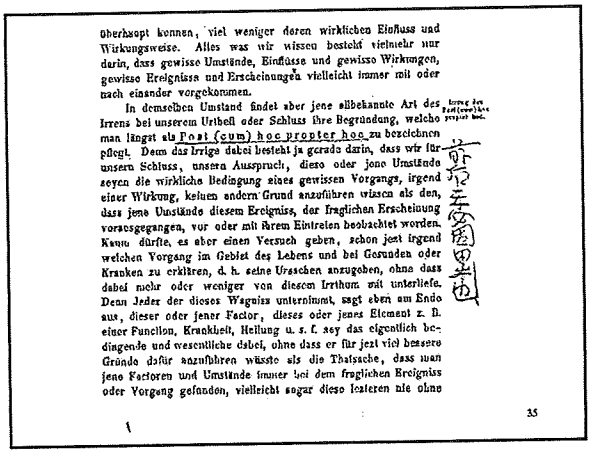
However, even before 1950, there had been a similar trial done in Japan by Dr. Kanehiro Takagi, the Director-General of the Department of Medical Service of the Japanese Navy.

This is an excerpt from an article that appeared in *The Lancet* in 1906. This was a prevention trial of beriberi among Japanese sailors on separate voyages of two Japanese navy ships in the South Pacific. The sailors on the first voyage by Rhujo in 1882 ate ordinary Japanese white rice. Out of the 376 soldiers, 179 caught beriberi with 25 deaths. The sailors on the second voyage by Tsukuba in 1884 ate Western food, consisting mainly of bread and meat. Out of 333, only 15 soldiers caught beriberi with no deaths. After the trial, Dr. Takagi ordered to change the sailors' food from white rice to western food, i.e. bread and meat. However, western food was very expensive at that time. So they substituted boiled wheat for boiled rice. The number of beriberi cases among navy sailors sharply decreased. He later became Baron. The trial, however, at that time was criticized by the army, represented by Dr. Rintaro Mori, who was studying hygiene in Germany at that time, and argued that the trial was not a concurrent comparison. He later became Director-General of the Department of Medical Service of the Japanese Army. He was also a very famous novelist with the penname Ogai Mori.



Slide 34 Dr. Mori's critical appraisal of Dr. Takagi's trial

Dr. Mori made a very critical appraisal of Dr. Takagi's trial. He said that the soldiers should have been divided into two—one group who ate wheat and the other who ate rice. Both groups should have been in the same place at the same time in order to avoid selection bias. Dr. Mori did not use the results of Dr. Takagi's trial. He insisted that Japanese army soldiers should eat white rice. However, because of his decision, several thousand Japanese army soldiers died during the two wars—the Sino-Japanese War and the Russo-Japanese War. Dr. Takagi was actually trained at the St. Thomas University under Dr. John Simon in London while Dr. Mori was trained in Germany under Dr. Max von Pettenkofer and Dr. Robert Koch.


überhaupt kennen, viel weniger deren wirklichen Einfluss und Wirkungsweise. Alles was wir wissen besteht vielmehr nur darin, dass gewisse Umstände, Einflüsse und gewisse Wirkungen, gewisse Ereignisse und Erscheinungen vielleicht immer mit oder nach einander vorgekommen.

In demselben Umstand findet aber jene allbekannte Art des Irrens bei unserem Urtheil oder Schluss ihre Begründung, welche man längst als Post (cum) hoc propter hoc zu bezeichnen pflegt. Denn das Irrige dabei besteht ja gerade darin, dass wir für unsern Schluss, unsern Ausspruch, diese oder jene Umstände seyen die wirkliche Bedingung eines gewissen Vorgangs, irgend einer Wirkung, keinen andern Grund anzuführen wissen als den, dass jene Umstände diesem Ereigniss, der fraglichen Erscheinung vorausgegangen, vor oder mit ihrem Eintreten beobachtet worden. Kaum dürfte, es aber einen Versuch geben, schon jetzt irgend welchen Vorgang im Gebiet des Lebens und bei Gesunden oder Kranken zu erklären, d. h. seine Ursachen anzugeben, ohne dass dabei mehr oder weniger von diesem Irrthum mit unterliefe. Denn Jeder der dieses Wagniss unternimmt, sagt eben am Ende aus, dieser oder jener Factor, dieses oder jenes Element z. B. einer Function, Krankheit, Heilung u. s. f. sey das eigentlich bedingende und wesentliche dabei, ohne dass er für jetzt viel bessere Gründe dafür anzuführen wüsste als die Thatsache, dass man jene Factoren und Umstände immer bei dem fraglichen Ereigniss oder Vorgang gefunden, vielleicht sogar diese letzteren nie ohne

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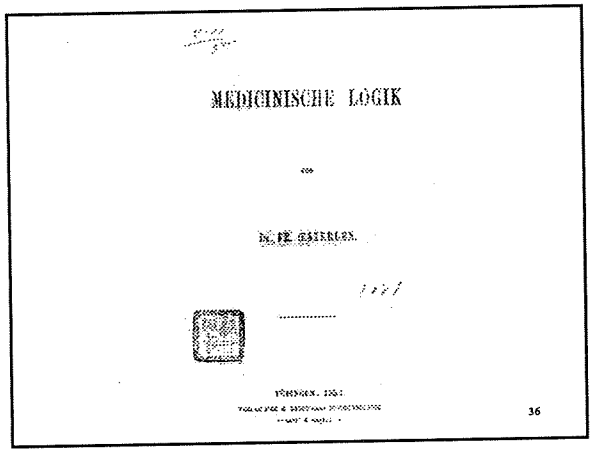
Slide 35-36 Post (cum) hoc propter hoc

In the Ogai collection at the General Library of the University Tokyo, I found the German book used by which Dr. Mori in his study of statistics and research methodology. In one page of the book, I found his underlined entries and notes he penciled in Chinese. It was a translation of the Latin phrase Post (*cum*) hoc propter hoc, which means "after it therefore because of it". The title of the book is Medicinische Logic by FR Oestelen, published in Tublingen in 1852. There is seal of Mori's collection on the inside front page. So he knew the logic of causality and he made a critical appraisal of Dr. Takagi's trial using his knowledge of it.


MEDICINISCHE LOGIK

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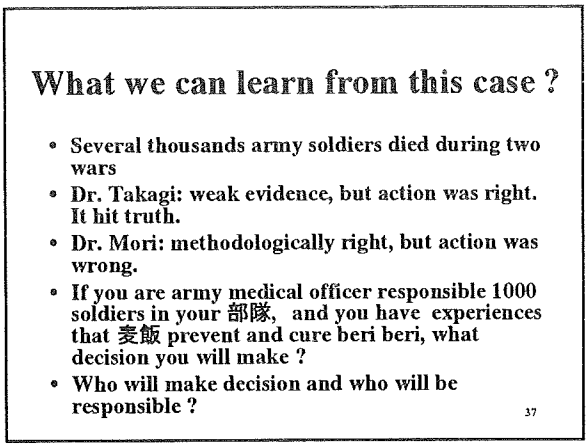
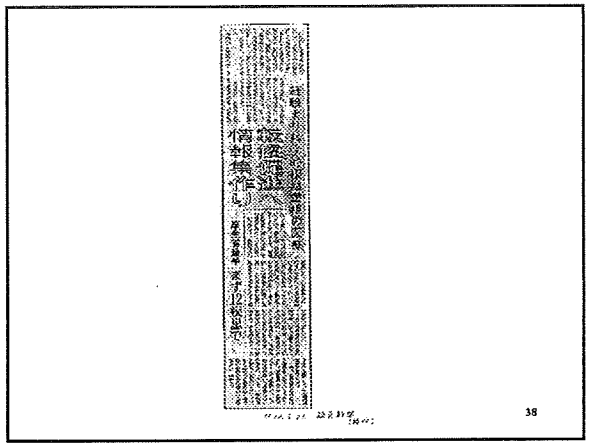


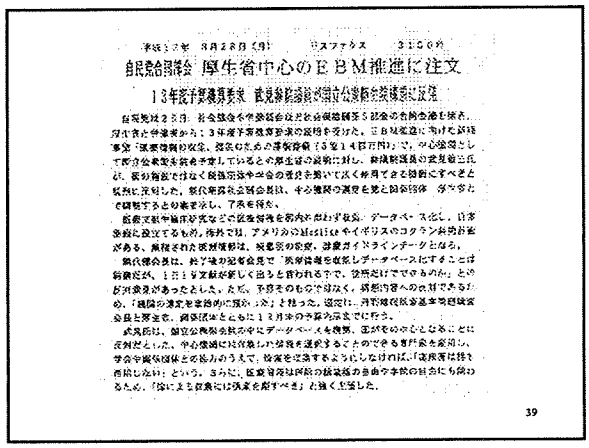
Slide 37 Lessons learnt from this case

What conclusions can we draw from this case? Several thousand army soldiers, who subsisted mainly on a Japanese rice diet, died. While Dr. Takagi's study brought out some significant results, it had weak evidence. The trial, of course, was not randomized because it was done before the concept of randomization was invented in the 1920s -1930s in the UK, by Dr. Ronald A. Fisher in the agricultural field. At the time of the trial, the cause of beriberi was unknown and some even considered it an infectious disease. While Dr. Mori was methodologically right—he argued that stronger evidence was needed—his action was wrong. So if you are an army medical officer responsible, for instance, for 1000 soldiers in your front, and you find yourself in such a situation, what decision would you make? If your decision was based on hard evidence, you might still make the soldiers eat white rice and they might die of the disease. So who should make the decision and who should be responsible for that decision-making?



Slides 38 Article from Yomiuri Shimbun

When the plan to establish an EBM Information Center in NIPH was announced, it was welcomed as a move towards clinical decision-making based on scientific evidence rather than experience. This is a newspaper article from the 21 August 2000 issue of *Yomiuri Shimbun*, which was welcomed by the public.



Slides 39 Article from medial fax news

This medical fax news of 28 August, published a week after the news in *Yomiuri Shinbun*, reported that LDP was against the plan.

Slides 40 Letter in Asahi Shimbun

This letter by Dr. Takahide Izumi, specialist in infectious lung diseases at the Kyoto University, appeared in the 25 October 2001 issue of *Asahi Shimbun*. He argued for the need for clinical practice guidelines.

Slides 41 Letter in Saitama Shimbun

This article, which appeared in the 26 October 2001 issue of Saitama Shimbun, reported that the Japanese Medical Association (JMA) did not like dealing with government-led activities. The EBM Information Center in NIPH, which will contain a database of Clinical Practice Guidelines was caught in a deadlock and was subsequently terminated.

Problems

- **Who will lead EBM movement in Japan ?**
  - **Government Organization (GO) or Non Governmental Organization (NGO)**
  - **Psychology**
- **Terminology**
  - **What guidelines means ?**

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Slide 42 Who will lead the EBM movement in Japan?

The question is: Who will lead the EBM movement in Japan? Will the leadership come from the Government side or the non-government side? Also, there is some psychological issue here. People all over the world do not like to be dictated upon by others. The same may be said of the JMA. Aside from this, there is also the problem of terminology, i.e., the different interpretations of guidelines in Japan.

Terminology

- August 2000
- meeting of 12 teams of development of clinical practice guidelines
- 治療ガイドラインclinical practice guidelines or 治療エビデンス集 (collection of evidence ?)

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Terminology

治療guidelines	治療evidence集
pre-appraised	self appraisal
時間短い	時間長い
制限的	自由

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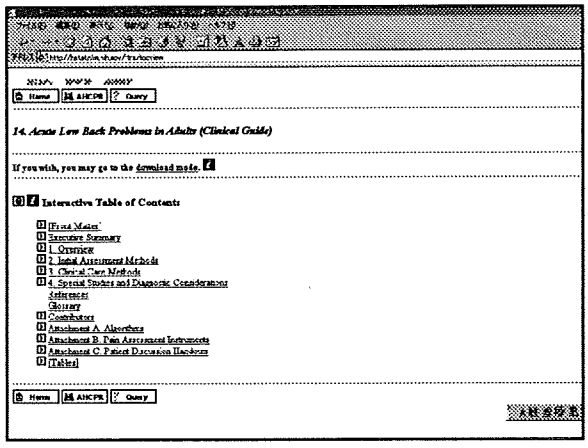


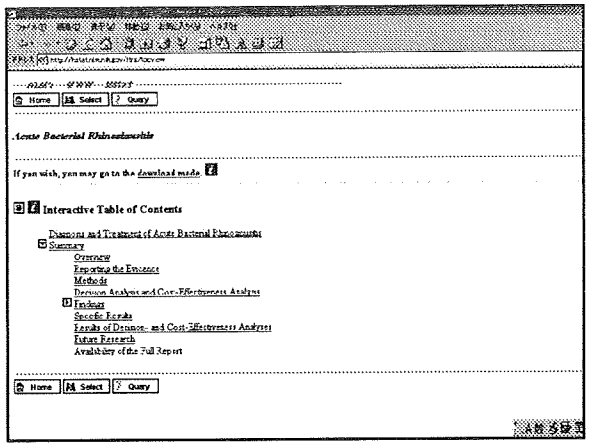
Slide 43-44 Terminology

There was a meeting at the Ministry of Health and Welfare (MHW) in August 2000 to discuss the intermediate evaluation of a draft version of the clinical practice guidelines developed using MHW funds. It also planned to conduct training on methodology of developing guidelines. Two each from the twelve teams responsible for developing guidelines were gathered in a session, where Dr. Tsuguya Fukui from Kyoto University, Dr. Toshiro Tango from NIPH and I served as trainers. Just before that meeting, we were told by one of the MHW staff that they would not use the term "clinical practice guidelines". He said they would just use the term "collection of clinical evidence", but the content was the same. The meeting between top officials of MHW and JMA reached the conclusion that the term "guideline" was too strong for JMA.

The guideline was a sort of pre-appraisal review. It was based on evidence-based pre-appraisal review. For the user it takes shorter time but it sounds too restrictive. While collection of clinical evidence allows physicians some kind of self-appraisal. Though it may take some time, physicians can nevertheless enjoy the freedom of choice as professionals.

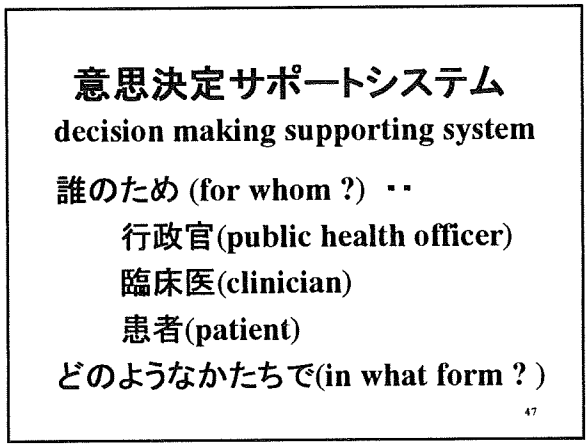
Slide 45 Example of Clinical Practice Guidelines by AHCPR

It is worthwhile to mention that similar incidents happened in the US a couple of years ago. This website includes a table of contents for the clinical practice guidelines on low-back problem in adults. This guideline, developed by the Agency for Health Care Policy and Research (AHCPR), was severely criticized by some orthosurgeons, who believed that the guidelines would reduce the number of surgery operations. They lobbied against it before the US Senate and the budget was drastically cut down. Thus the development of clinical practice guidelines by professionals was stopped. AHCPR was renamed to Agency for Healthcare Research and Quality (AHRQ) in 1999, and now AHRQ is developing evidence reports instead.



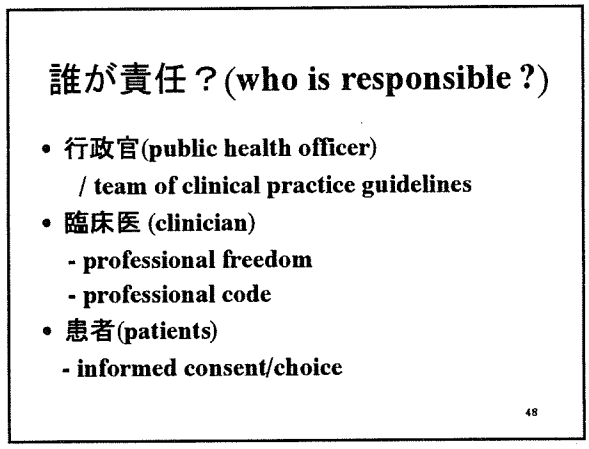
Slide 46 Example of Evidence Report by AHRQ on Acute Bacterial Rhinosinusitis

This is the table of contents for the evidence report on acute bacterial rhinosinusitis. The systematic review and the development of the report was conducted by Dr. Lau's group. Unlike the guidelines there is no clear recommendation in the evidence reports, which always end with the same conclusion, i.e., further studies are needed.



Slide 47 Decision-making support system

The development of guidelines or evidence collection/report is part of a decision-making support system. But you also have to consider for whom these reports are made. Are they for the public health officer, clinician, or patient? In what form will they be provided and how many health sectors will be involved in the development and distribution?



Slide 48 Who is responsible?

Also, who will be responsible for this decision-making? As I mentioned to you earlier, if you were an army medical officer, you had to make a decision. Public health officers or those involved in guideline development may take responsibility. Physicians also may take responsibility, at the same time claiming professional freedom. But the professional code among physicians is seldom argued, which is a weak point in Japan and therefore has to be improved. Nowadays in Japan, patients want more information. Patients may also take responsibility based on their autonomy. That is why we now have informed consent or informed choice.

Conclusion

This is my analysis of the current situation, or at least the last 5 years of the EBM movement in Japan. It has been decided that major health care reform will take place in FY 2002 in Japan. I hope that within the next one year and beyond, all the conflicting issues of EBM will be resolved and a system established which will serve the people's health.

Thank you.

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