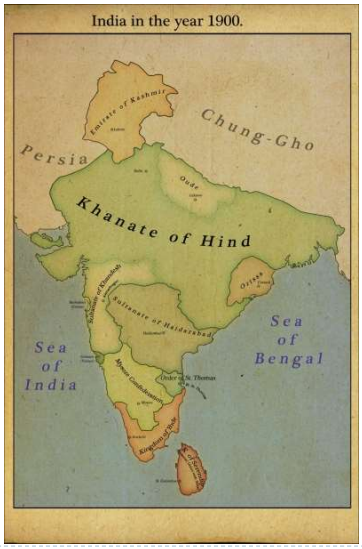
# Rational drug design lecture 2

Łukasz Berlicki

## Three princes of Serendip

## Serendipity

- Serendip – Sri Lanka
- **The three princes of Serendip** – Persian fairytale
- The word was used for the first time on 28.01.1754 by Horace Walpole in letter to Horace Mann.




## Serendipity

- natural ability to interesting and valuable discoveries by chance;
- the gift of finding valuable or pleasant things, which are not searched for;
- „by serendipity" = „by chance";
- happiness, success

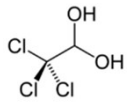
## Serendipity

- *Dans les champs de l'observation le hasard ne favorise que les esprits préparés.*

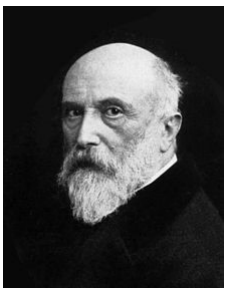
  **Luis Pasteur**

## Chloral

- Obtained by Justus von Liebig, 1832
- $H_3CCHO + 3\ Cl_2 + H_2O \rightarrow Cl_3CCH(OH)_2 + 3\ HCl$



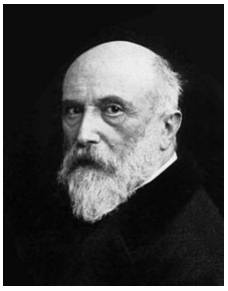

- Oscar Liebreich applied it as hypnotic drug (inducing sleep) thinking that it will release chloroform in human body, 1869.



Oscar Liebreich

## Chloral hydrate


$Cl_3CCHO + NaOH \rightarrow Cl_3CH + HCOONa$



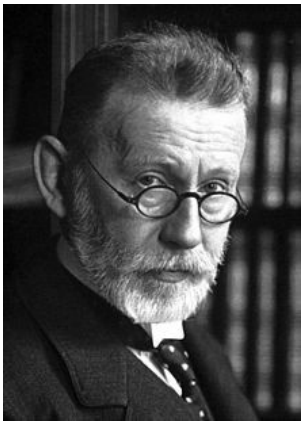
Oscar Liebreich

- Trichloroethanol is GABA receptor agonist (similarly to barbiturans and ethanol).
- Chloral hydrate is first synthetic hypnotic drug and it is still in use (since 150 years).

## Chemotherapy

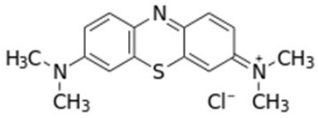
- Paul Ehrlich,
  born1854, Strzelin
  studies in Wrocław (Breslau)
  1908, Nobel Prize
  died,1915

**Chemotherapy** – medical treatment using chemical compounds (currently, the term is used exclusively in oncology).

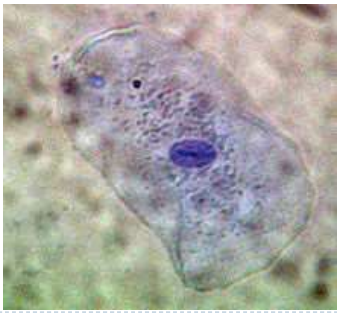


## Cell staining

- Observation: Some dyes are staining selectively some tissues. This means that such compounds interacts specifically with some types of cells.
- Hypothesis: it is possible to find compounds that ineracts specifically with chosen pathogens. 'Magic Bullet'
- Methylene blue is staining cells of parasites responsible for malaria.

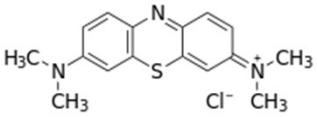



Methylene blue



## Malaria

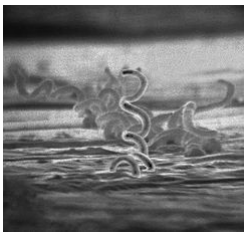
- Paul Ehrlich has cured one patient from malaria using methylene blue, but more detailed studies showed that this compound is not effective.



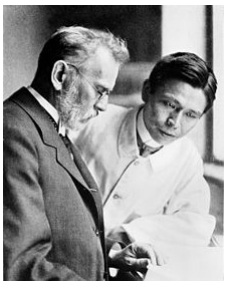

Methylene blue

## Syphilis

- In XIX/XX c. ca. 15% of population of large cities was infected with Syphilis.
- The only possible treatment used inorganic mercury salts.



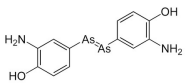
*Treponema pallidum*

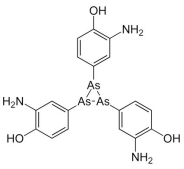


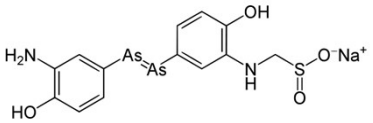
Paul Erlich and Sachahiro Hata tested several hundreds of arsenoorganic compounds against Syphilis.

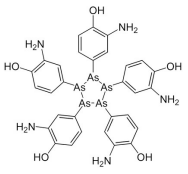
## Syphilis

- Compound no 606 showed activity and was introduced to the market as Salvarsan.
- Next studies allowed finding compound with better solubility in water - Neosalvarsan (no 947).
- It was the first high-throughput screen.









## Penicillin

- Alexander Fleming
- Fleming was searching for a drug against bacterial infections for years. He studied various species of bacteria.
- About half of 10 mln victims of WW1 died due to infections.
- Nobel Prize 1945

## Penicillin

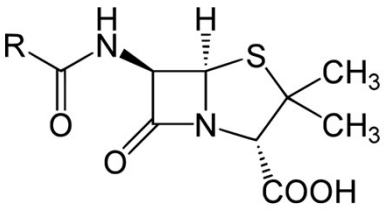
- In July1928, Fleming left ca. 50 plates with *Staphylococcus aureus* and went for vacations.
- He was back in September and before washing plates, he studied them. On some of plates, there was a molt, which caused inhibition of bacterial growth.

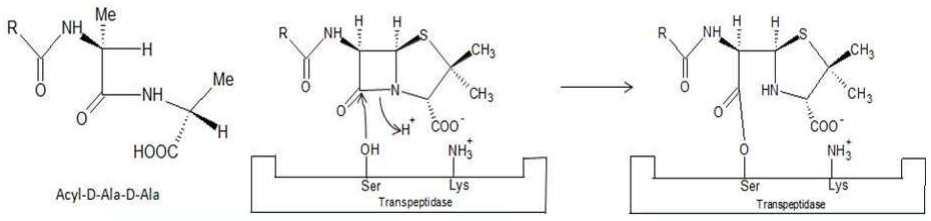
## Penicillin

- The molt was very rare organism – *Penicillium notatum*, which came from mycological laboratory one level below (where molts from asthma patients was studied).
- The weather was also favoring this discovery. High temperatures came just after inspection of plates and *Penicillium notatum* could grow efficiently.
- The solution isolated from molt was antimicrobial even at 1:800 dilution.
- Fleming has not shown that penicillin is active *in vivo*.

## Penicillin

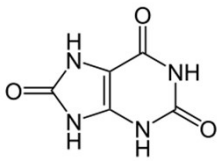
- Penicillin is inhibitor of D-Ala-D-Ala transpeptidase



## Lithium salts

- In 1859 Alfred Garrod introduced treatment of gout (podagra) using lithium carbonate, which was able to dissolve deposits of uric acid.

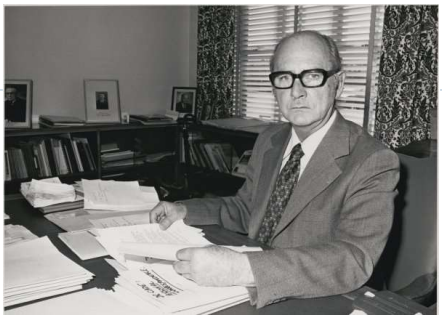

## Lithium salts

- In second half of XIX c. it was believed that uric acid or urea can form deposits in brain and cause changes in behavior (depression/mania).
- William Hammond (New York) and Carl Lange (Denmark), used successfully lithium salts for these indications.

William Hammond

Carl Lange

## Lithium salts



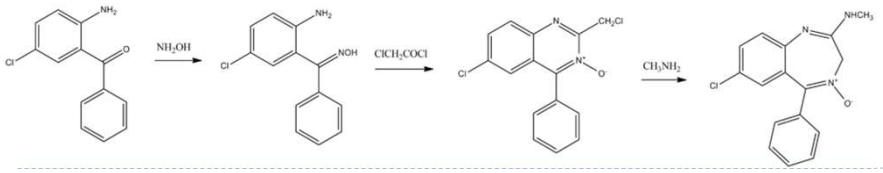
- John Cade, Australia:
- Hypothesis: mania is the state of poisoning by excess of some metabolite while depression is lack of this metabolite.
- Hypothesis test: toxicity of urine of patients with mania was more toxic to Guinea pigs than urine of healthy humans. It was attributed to higher concentration of urea or uric acid.
- Test confirmation: studied of toxicity of urine with additional amount of uric acid.
- Result: addition of lithium salt of uric acid causes loss of toxicity.

## Lithium salts

- 0.5% solution of lithium carbonate causes lethargy of Guinea pigs
- It was evidenced that $Li_2CO_3$ is effective for control of manic-depressive psychosis
- In order to apply lithium salts safely, it is necessary to monitor the level of lithium in blood.
- Previously, mental illnesses were treated using electroshocks and lobotomy.

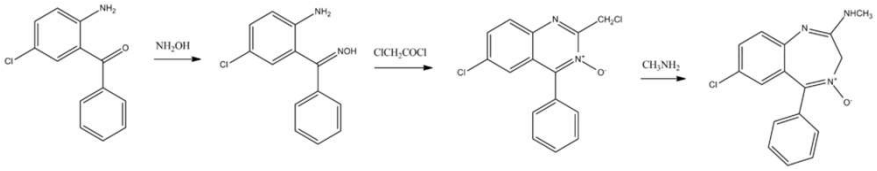
# Librium and Valium

**Leo Sternbach** –
Born: 1907 Croatia,
Childhood in Austria,
High school Bielsko Biała, Poland,
Pharmaceutical studies, Kraków, UJ,
1931 – PhD in Chemistry (prof. K. Dziewoński) UJ,
1937 – Zurich, prof. L. Ruzicka,
1940 – work Hofman La Roche,
Died: 2005 USA.

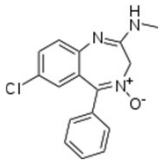



# Librium and Valium

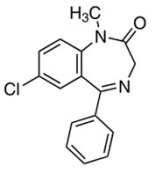
Initially obtained ca. 40 benzdiazepines, but none was active.
Derivative with methylamine was put on shelf.
Compound Ro 5-0690 went to pharmaceutical tests after cleaning of laboratory.



## Librium and Valium




Librium




Valium

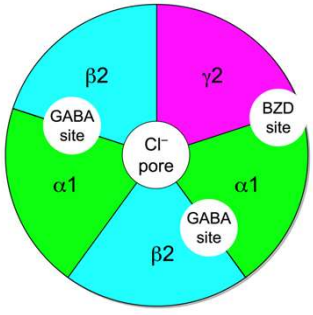
- These compounds shows sedation, anxiolytic and anticonvulsant effects
- Increases GABA receptor action by binding to $GABA_A$ receptor
- Both obtained by Leo Sternbacha

## Librium and Valium

- In 60- and 70-ies use of Valium was out of the control and the drug was used widely for helping in troubles of everyday life.
- The Rolling Stones presented song *Mother's Little Helper* about housewives using Valium.
- 2.3 billion of pills was sold in 1978.
- Considerable amounts of Valium were taken by Elvis Presley, Elizabeth Taylor, Andy Warhol.

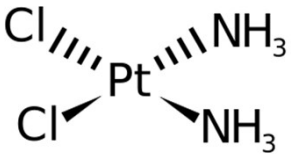
## Librium and Valium

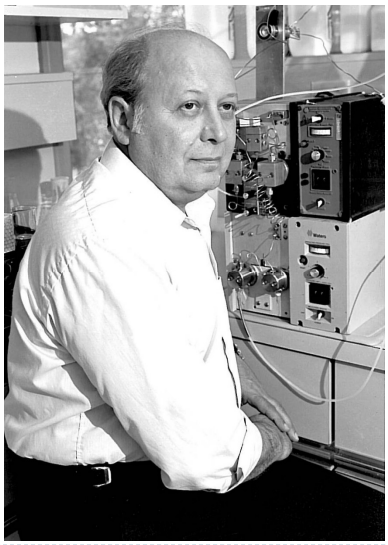
- Benzdiazepines are binding to $GABA_A$ receptor which controls the $Cl^-$ ions flow.
- Benzodiazepines do not interact with GABA binding but increases $Cl^-$ ions flow.
- This causes increase of potential necessary to excitation of the neuron.
- It have tranquilising effect on neurons.



## Cis-platinum

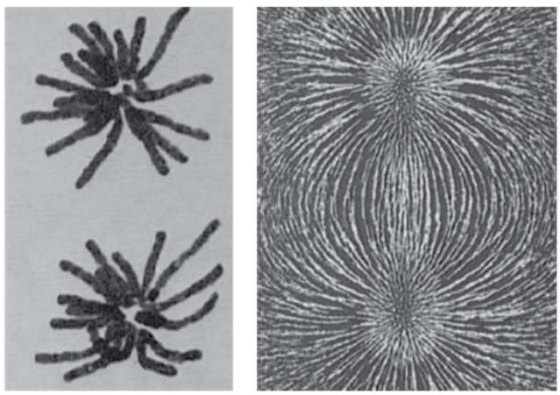
- Barnet Rosenberg, 1965.
- Discovery of cis-platinum



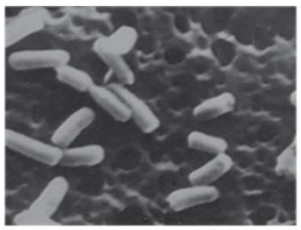
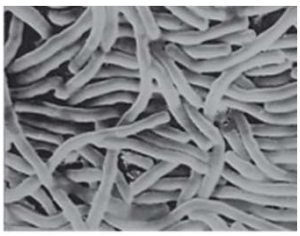
## Cis-platinum

- Hypothesis: Lines of magnetic field are similar to cells during mitosis, thus magnetic field influences cell division.



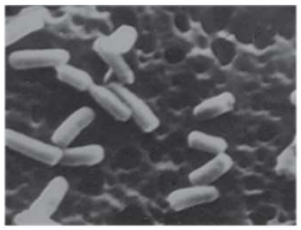
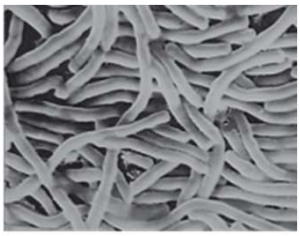
## Cis-platinum

- Experiment: *E. coli* cells were put in the electromagnetic field generated by platinum electrodes.
- Result: Growth of cells was without changes, but cells stopped their division.

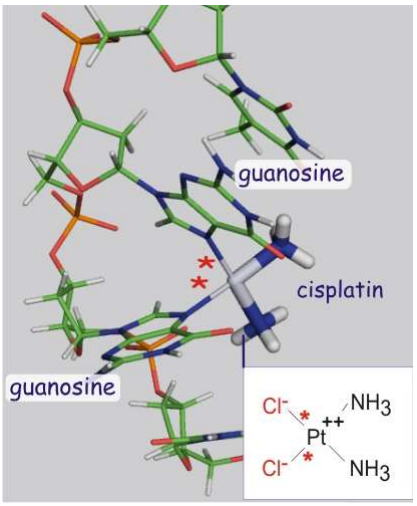
## Cis-platinum

- Conclusion: the product of electrolysis of Platinum electrodes influences cell division. Cis-platinum is obtained in solution of ammonium chloride.
- Cis-platinum showed very high anticancer activity.

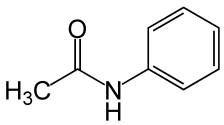
## Cis-platinum

- Cis-patinum binds to two guanosine residues in DNA and influences mitosis. This activates the process of apoptosis.



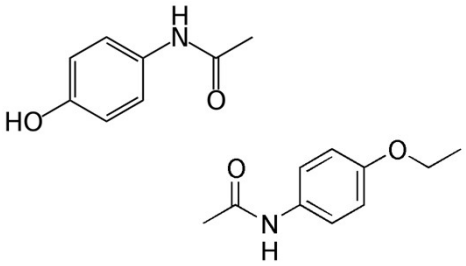

## Paracetamol

- Cahn and Hepp has been working on the possibility of application of naphtalene as internal antiseptic. The theraphy was not effective.
- But, it was shown that it acts as analgesic (against pain) and antipyretic (against elevated body temperature) in case of some patients.
- Detailed tests indicated that it was an error of pharmacy supplying product. The acetanilide was send instead.
- Acetanilide was the first analgesic and antipyretic synthetic compound (1886, Cahn, Hepp).



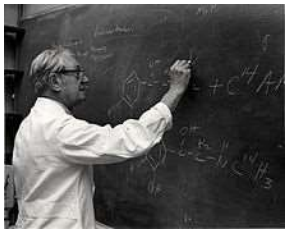
## Paracetamol

- Acetanilide showed side effects – methemoglobinemia
- In 1893, von Mering analyzed derivatives of acetanilide – paracetamol and phenacetin. He showed that paracetamol causes methemoglobinemia while phenacetin does not.
- Phenacetin was introduced to the market by Bayer.

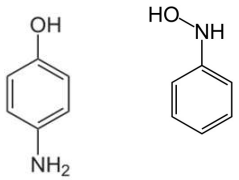



## Paracetamol

- In 1947, it was evidenced that paracetamol is the major metabolite of acetanilide in human blood.
- It was also evidenced that paracetamol does not causes methenoglobinemia.
- Also phenacetin is metabolized to paracetamol.
- Methenoglobinemia is caused by phenylhydroxylamine, which is formed from contaminating *p*-aminophenol.

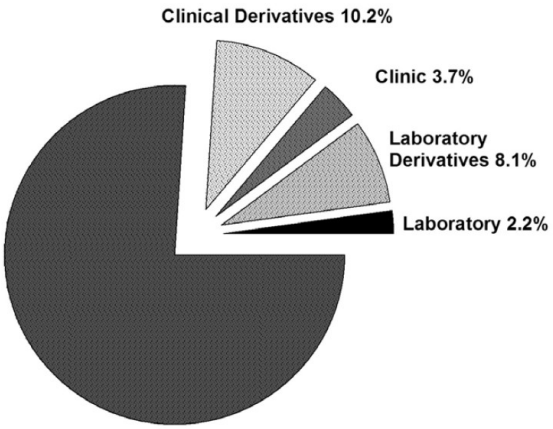


Julius Axelrod
Bernard Brodie



# Serendipity

- Discovery of ca. 25% of drugs was related to ‚serendipity'.




# The list of drugs discovered by serendipity

| Laboratory Drugs | Reference | Number of Derivatives | Application |
|---|---|---|---|
| Acetanilide | a(p.438) ,b | 1 | Antipyretic |
| Acetohexamide | a(p.393),b, c(p.184) | 8 | Diabetes II |
| Captopril | a(p.281), c (p.88) | 8 | Cardiovascular |
| Cisplatin | a(p.63), b, c(p.10), d(p.136) | 2 | Cancer |
| Diethylstilbestrol | a (p.196), b | 1 | Hormonal |
| Digoxin | a(p.39), c(p.84) | 4 | Cardiovascular |
| Ergotamine | a (p.341), c(p.159), d(p.296) | 6 | Cardiovascular |
| Ephedrine | a (p.100) | 9 | CNS |
| Griseofulvin | a (p.297), b | 0 | Antifungal |
| Heparin | a (p.269), b, d(p.234) | 4 | Cardiovascular |
| Isoniazid | a (p.396), b | 0 | Antibiotic |
| Lidocaine | a (p.434) | 6 | CNS |
| Lithium | a (p.62), b, c(p.140), d(p.261) | 0 | CNS |
| Marinol | a(p.111) | 1 | CNS |
| Mechlorethamine | a(p.440), b, c (p.8), d(p.122) | 5 | Cancer |

## The list of drugs discovered by serendipity

| | | | |
|---|---|---|---|
| Mecillinam | a (p.323) | 1 | Antibiotic |
| Methotrexate | a (p.249), c(p.18) | 1 | Cancer |
| Nalidixic Acid | a (p.394), c (p.69) | 8 | Antibiotic |
| Nitroglycerine | a (p.433), b, c (p.80) | 2 | Cardiovascular |
| Penicillin | a (p.289), b, c(p.54), d(p.59) | 21 | Antibiotic |
| Pentamidine | a (p.277) | 0 | Antiprotozoal |
| Physostigmine | a (p.96) | 0 | Ocular |
| Quinine | a (p.77) | 1 | Antiprotozoal |
| Sorafenib | d (p.163) | 0 | Cancer |
| Streptomycin | c (p.63), d (p.86) | 7 | Antibiotic |
| Sulfanilamide | a (p.384), c (p.50), d(p.54) | 13 | Antibiotic |
| Valproic acid | a (p.444),b | 1 | CNS |
| Vinblastine | a (p.102), c(p.12), d(p.133) | 3 | Cancer |
| Dicoumarol | a (p.111), b, d (p.236) | 0 | Cardiovascular |
| Warfarin | a (p.137), b, d (p.237) | 3 | Cardiovascular |
| Zinc Sulfate | a (p.62) | 0 | Wilson's disease |

## Types of ‚serendipity'

- Finding something entirely different than someone has been searching for.
- False hypothesis leads to new results;
- Someone finds new indications than she/he was searching for.

- In laboratory studies
- In clinical studies

# New studies

## Discovery of an α-Amino C–H Arylation Reaction Using the Strategy of Accelerated Serendipity

Andrew McNally, Christopher K. Prier, David W. C. MacMillan*

Serendipity has long been a welcome yet elusive phenomenon in the advancement of chemistry. We sought to exploit serendipity as a means of rapidly identifying unanticipated chemical transformations. By using a high-throughput, automated workflow and evaluating a large number of random reactions, we have discovered a photoredox-catalyzed C–H arylation reaction for the construction of benzylic amines, an important structural motif within pharmaceutical compounds that is not readily accessed via simple substrates. The mechanism directly couples tertiary amines with cyanoaromatics by using mild and operationally trivial conditions.

Accidental or serendipitous discoveries have led to important breakthroughs in the chemical sciences. With regard to bond-forming reactions, such fundamental synthetic transformations as Friedel-Crafts, Wittig olefination, and Brown hydroboration reactions were found when the objectives of the initial experiments were not in accord with the observed outcomes (*1*).

Recently, we questioned whether serendipity could be forced or simulated to occur on a predictable basis in the realm of reaction discovery, thereby providing a reliable platform to access valuable transformations or unexpected pathways. Herein, we describe the successful execution of these ideals and describe a fundamentally distinct C–H functionalization-arylation reaction that we expect will be of broad use to practitioners of chemical synthesis and, in particular, medicinal chemistry.

Assuming that serendipity is governed by probability (and thereafter manageable by statistics), performing a large number of random chemical reactions must increase the chances of realizing a serendipitous outcome. However, the volume of reactions required to achieve serendipity in a repetitive fashion is likely unsuitable for traditional laboratory protocols that use singular experiments. Indeed, several combinatorial strategies have previously been used to identify singular

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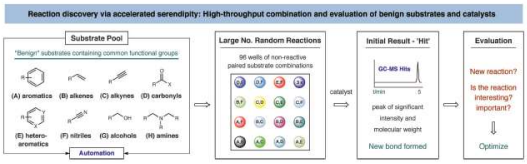


**Fig. 1.** Approach to reaction discovery without preconceived design via the concept of accelerated serendipity. R indicates a generic organic substituent; X and Y, heteroatoms.



# Summary

- 'Serendipity' is one of most important aspects of new drugs discovery.
- Considerable number of drugs (in particular older ones) was found by chance.
- „Discovery needs luck, invention, intellect—none can do without the other."

Wolfgang Goethe

## For those who are interested in

- Movie on discovery of lithium salts by J. Cade:
- **Troubled Minds: The Lithium Revolution**
- Book:
- **„Happy Accidents: Serendipity in Major Medical Breakthroughs in the Twentieth Century**", M. Myers