

Directions in Clinical Chemistry and Laboratory Medicine

David E Bruns, MD

**Professor of Pathology
Director of Clinical Chemistry
Associate Director of Molecular Diagnostics
University of Virginia
Charlottesville**



Thomas Jefferson



Monticello
Charlottesville



Jefferson Memorial,
Washington, DC



University of Virginia
Hospital



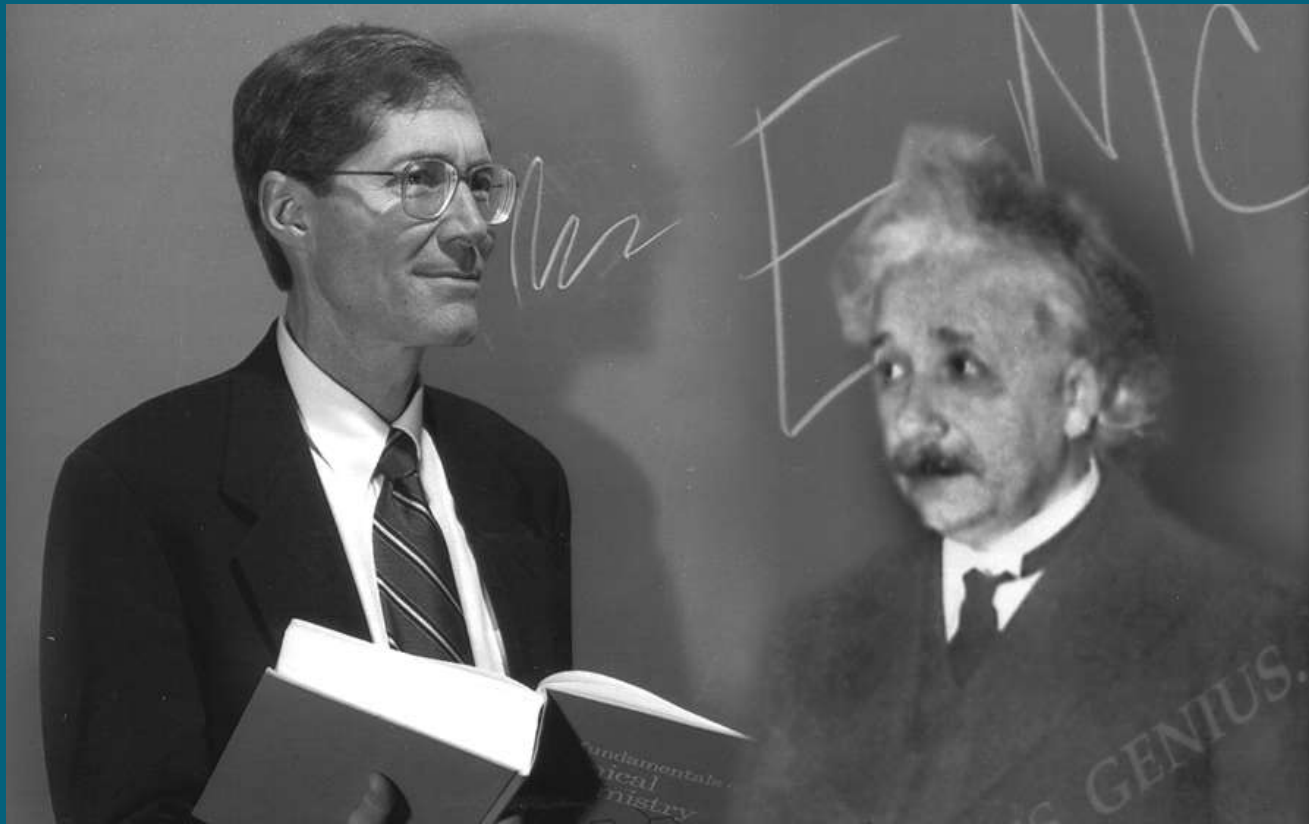
Charge

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...a reflective and thought-provoking talk on 'Directions in Clinical Chemistry and Laboratory Medicine'

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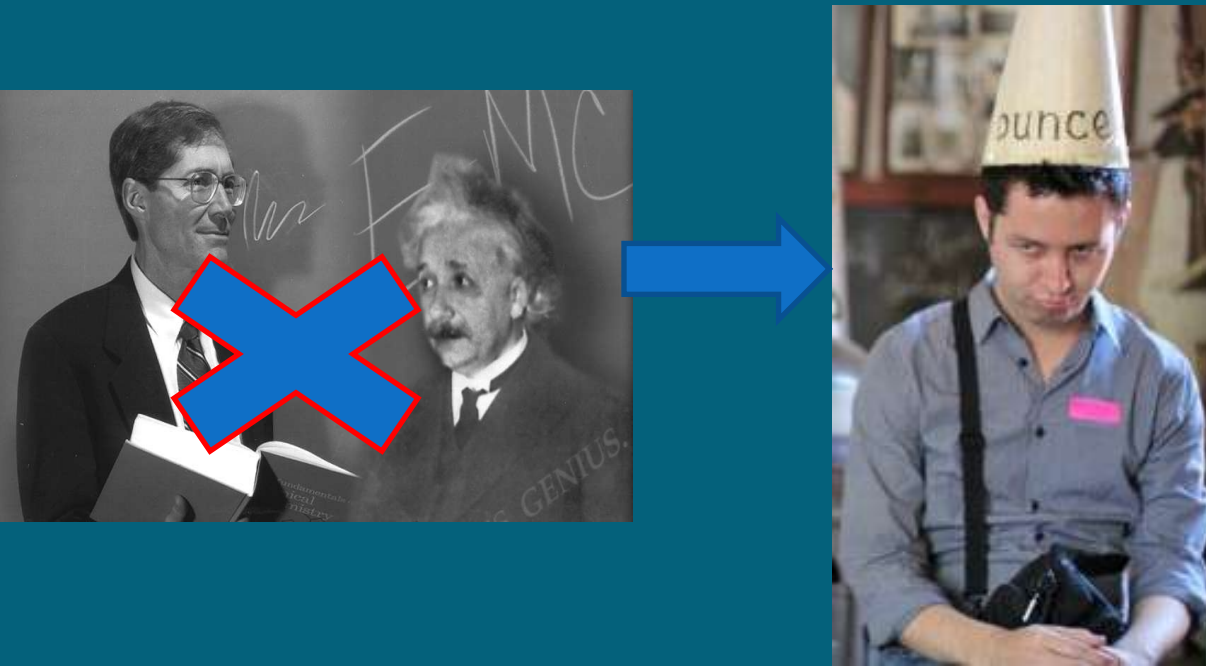
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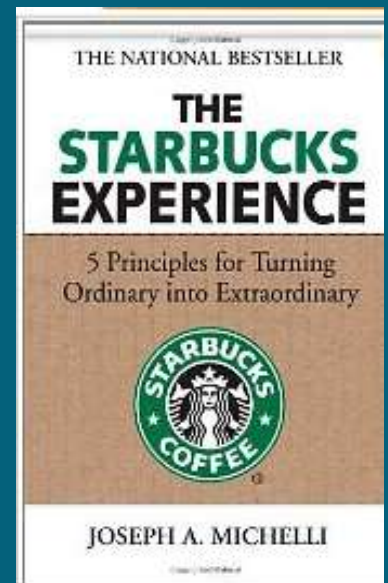
...but for a distillation of experience

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...a reflective and thought-provoking talk on 'Directions in Clinical Chemistry and Laboratory Medicine'

... we are not looking for lots of high powered science

...but for a distillation of experience



Charge

- ...a reflective and thought-provoking talk on 'Directions in Clinical Chemistry and Laboratory Medicine'
- ... we are not looking for lots of high powered science
- ...but for a distillation of experience
- perhaps with a touch of humour.

My Experiences

- Chemist, Sigma Chemical Company
- Editor, *Clinical Chemistry*
- Director of Clinical Chemistry, Founding Co-Director of Molecular Diagnostics Lab.

Clinical Chemistry Before And During My Days At Sigma in the 1960s

- Laboratories bought instruments from instrument companies and chemicals from chemical companies.
- Sigma sold chemicals.
- By the 1960s, some companies, like Sigma, sold reagents and kits to hospital laboratories.

A One-Slide History of Sigma Chemical Company

- Lou Berger purified ATP in the Cori lab and went to Sigma.
- ATP was Sigma's first product – 1 of 5 products in first catalog.
- The Coris' son, Tom, later became president of Sigma.

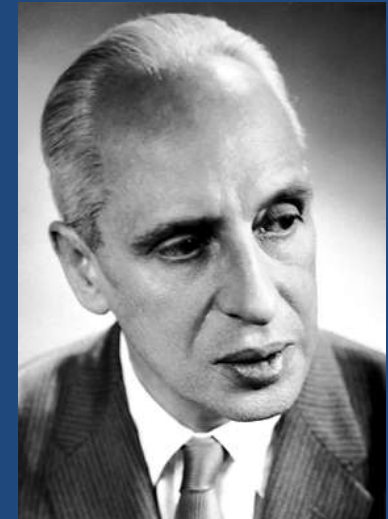
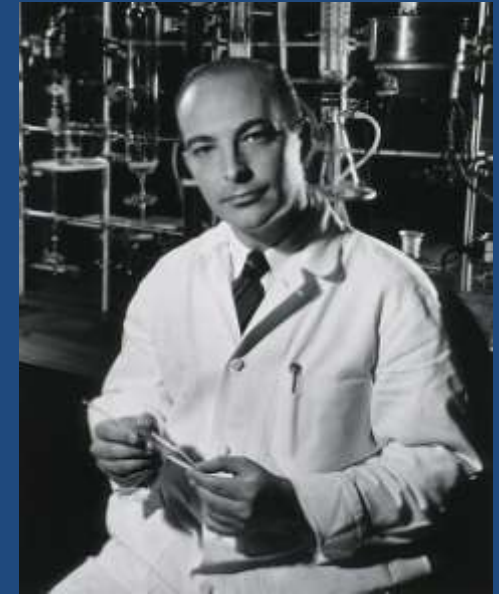
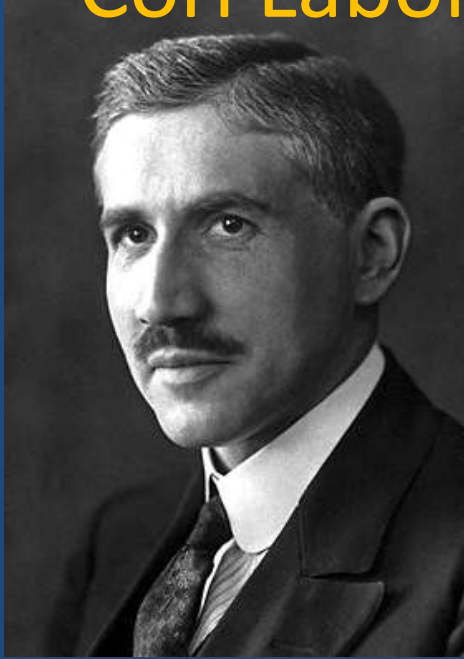


Carl and Gerty Cori



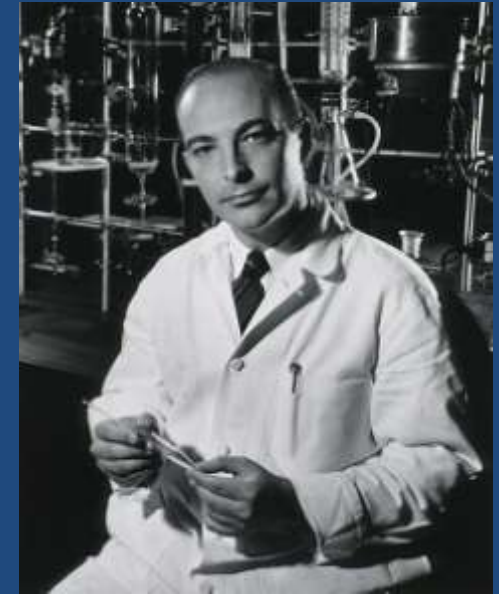
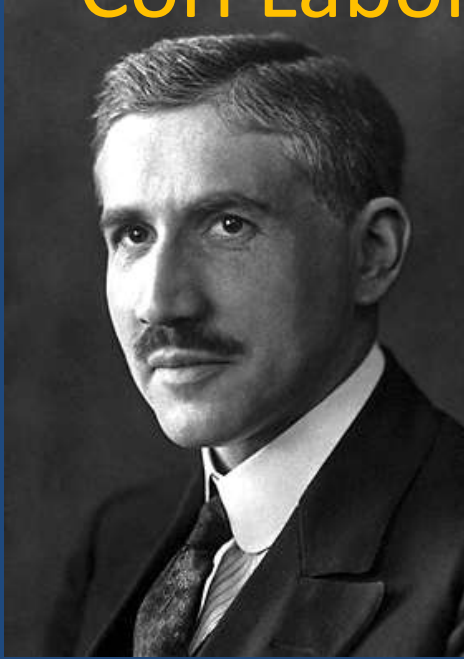
Tom Cori, PhD

Some of the Biochemists from the Cori Laboratory Who Used Sigma Chemicals

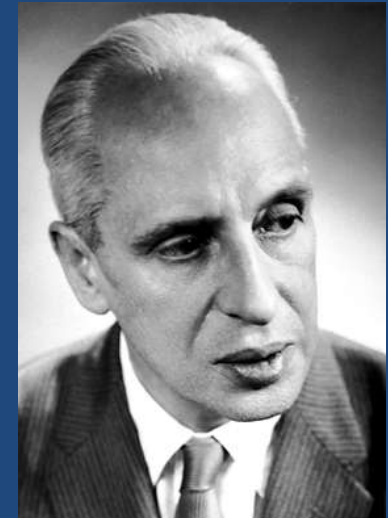


Otto Meyerhoff, Severo Ochoa,
Arthur Kornberg, Carl and Gerty Cori.

Nobel Laureates from the Cori Laboratory Who Used Sigma Chemicals



Otto Meyerhoff, Severo Ochoa,
Arthur Kornberg, Carl and Gerty Cori.



My Job Interview at Sigma Chemical Company

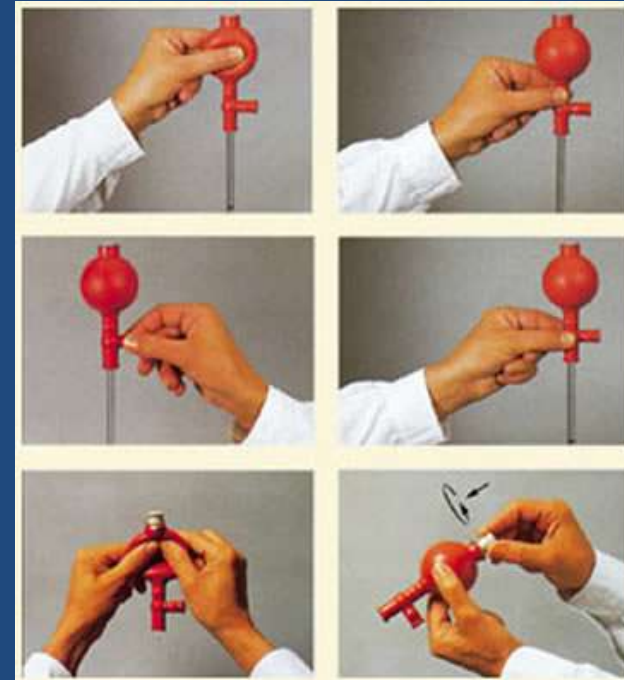
Lou Berger: “What is the Henderson-Hasselbach equation?”

Bruns: “ $\text{pH} = \text{pK} + \log \text{ of salt over acid.}$ ”

Lou Berger: “Very good. You would be surprised at how many PhD’s cannot answer that question.”

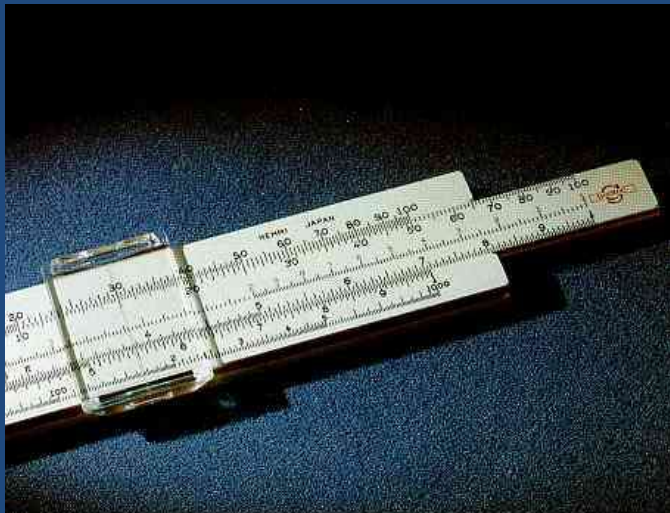
[Bruns, aside: “I might be surprised, but not as surprised as I am that I got the right answer.”]

Some of the High- Tech Equipment That I used at Sigma

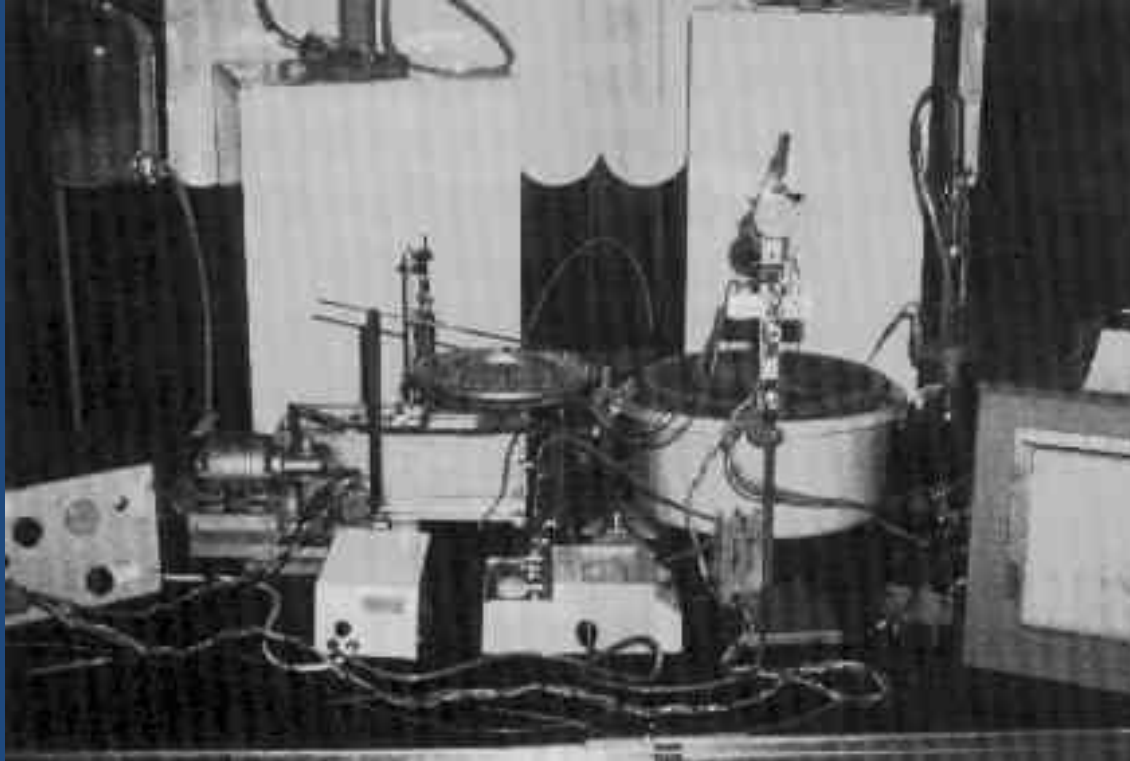




More High-Tech Equipment That I used at Sigma

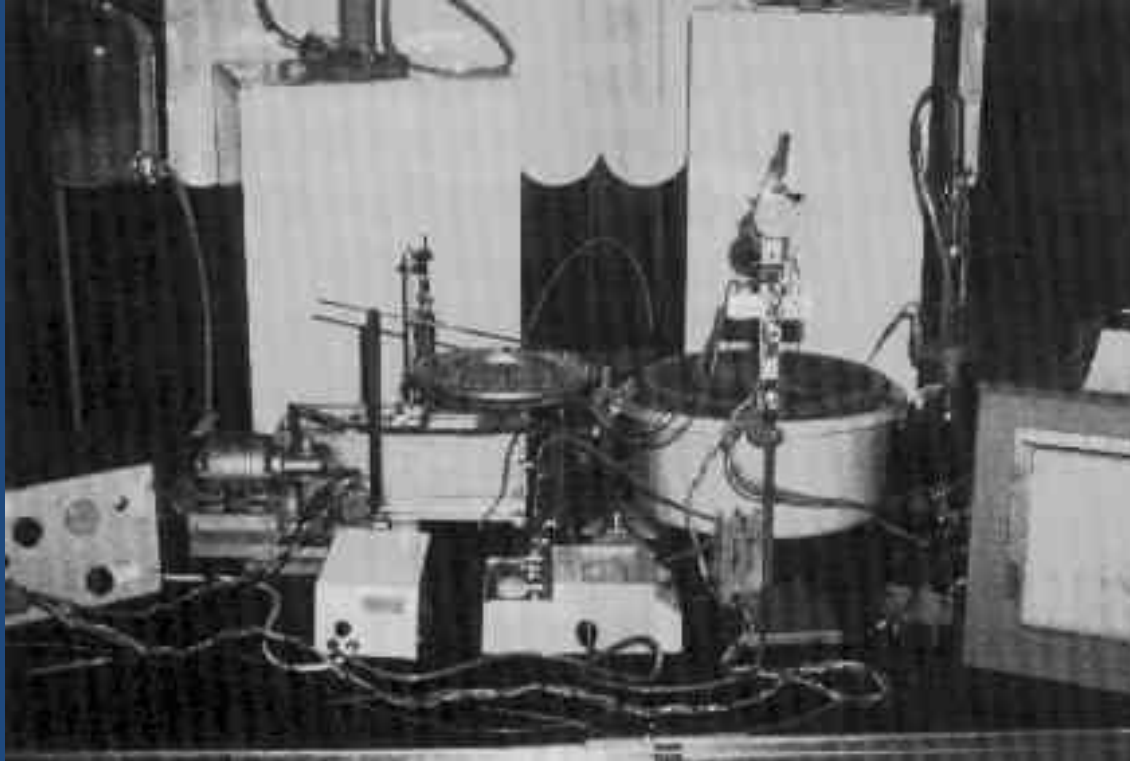


AutoAnalyzer

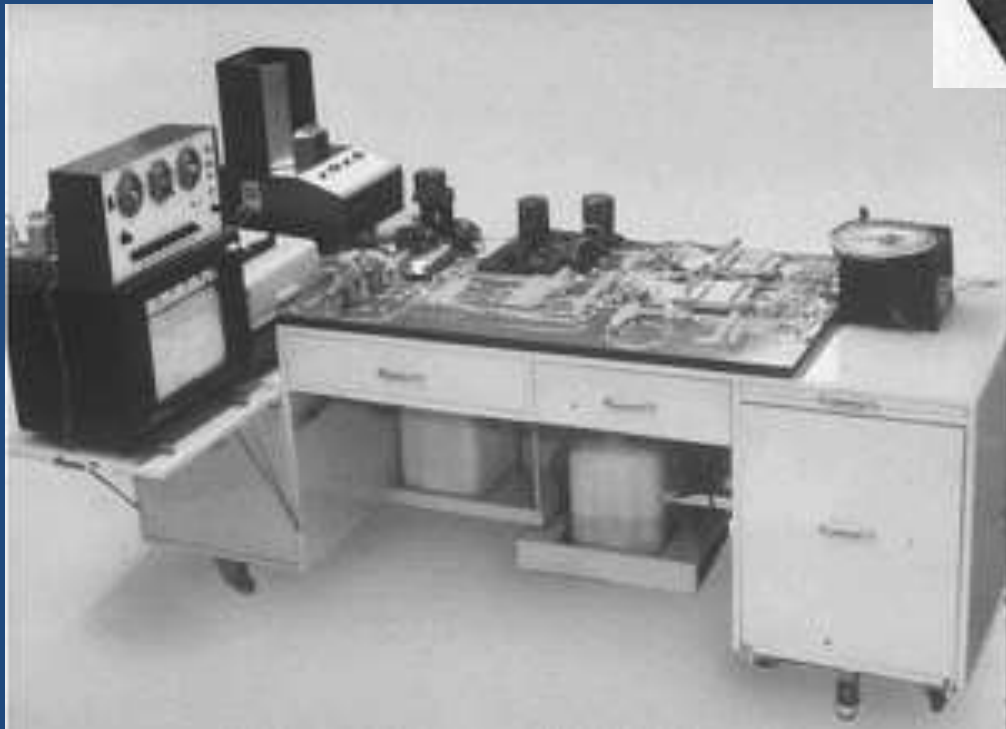
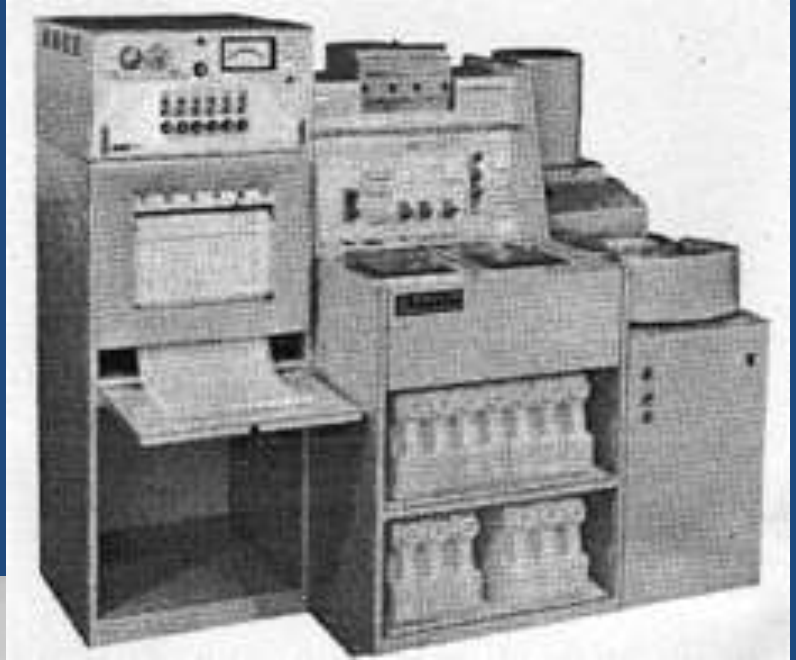


Technicon Corp.

AutoAnalyzer



Technicon Corp. provided analyzer AND reagents.
Sigma sold no analyzers, only chemicals and reagents.





Hormones

- Bioassays until 1960s
 - Insulin:
 - Fall in rat blood sugar (whole animal bioassay)
 - Rate of glucose oxidation in rat epididymal fat pad

Hormones

Pregnancy test (Bioassay for hCG)

- Inject woman's urine into rabbit, kill rabbit, examine ovaries.
- Many people believed, erroneously, that urine from a pregnant woman killed the rabbit.
- "The rabbit died" meant that the test was positive.



There is a better test.

House (TV Show)

Dr House:

Do the pregnancy test. It doesn't take much time and “we no longer kill rabbits.”

Radioimmunoassay

Rosalyn Yalow, PhD, physics

- 1960: RIA for insulin (1st manuscript rejected)
- ACTH, gastrin, PTH, growth hormone and others followed
- 1972: Berson dies
- 1977: Nobel Prize for Yalow

“Rarely have so many had so few to thank for so much”.



Solomon Berson, MD



Immunochemical Assays

- Major advances in endocrinology
- Clinical chemists replaced radioactivity with more-sensitive labels.
- Assays were automated and far more precise.

JESSE ROTH



BEP MURPHY



IRA PASTAN



ROBERT
LEFKOWITZ



Evolution

Chemical & Immunochemical Assays

Organic Synthesis, rabbits,
radioactivity; manual tests → →

Reagent sets (kits) → →

Mechanized /Automated
SYSTEMS with reagents → →

Random access testing, Electronic
reporting from bar-coded
samples...

Molecular Diagnostic Testing

- Watson and Crick, NIH funding
- Clinical applications initiated in various sections of laboratory medicine, especially microbiology and chemistry.
- *Clinical Chemistry* adds headings in TOC for “Molecular Diagnostics”
- “Tietz Textbook of Clinical Chemistry” becomes “Tietz Textbook of Clinical Chemistry and Molecular Diagnostics”.

Evolution

Chemical & Immunochemical Assays

Organic Synthesis, rabbits, radioactivity; manual tests → →

Reagent sets (kits) → →

Mechanized /Automated SYSTEMS with reagents → →

Random access testing, Electronic reporting from bar-coded samples...

Molecular Diagnostics Testing

Bacteria to Make Reagents; manual tests (LDT) → →

Reagent sets (RUO, ASRs)

Mechanized /Automated SYSTEMS with reagents → →

Random access testing, Electronic reporting from bar-coded samples...

Point of Care Testing

Blood Glucose Meters, 1970

US



Japan



Glucose Meters

FreeStyle Freedom



Register Your Meter Online

NO MORE FINGER STICKING!

TrueIrock
12-01 5:36
102

...st the Basics of Testing
NOW IN COLORS!



- ▶ Home Delivery, No Charge for Shipping
- ▶ No Up-Front Costs.*
- ▶ No Claim Forms to Fill Out.
- ▶ Personalized Support

FREE GLUCOSE METER

Performa

BLOOD GLUCOSE METER AND LANCING DEVICE



- **DEPENDABLE, WORRY-FREE TESTING**
- **FAST 5-SECOND TEST**
- **SMALL SAMPLE SIZE**



Computers

- Laboratory information systems nonexistent until 1970s
- Justification was based on dollars.
- More later.

Clinical Chemistry, The Journal

Clinical Chemistry, The Journal

- I was publishing in J Biol Chem, Am J Physiol, etc.
- Editorial Board of Clin Chem.
 - Elected (Thanks to John Savory et al)
- Executive Committee of Ed. Board:
 - Donald Young
 - Jack Ladenson
 - Carl Burtis

Editing

- “Mostly in-doors, no heavy lifting.
- “You will learn a lot...
about human nature.”

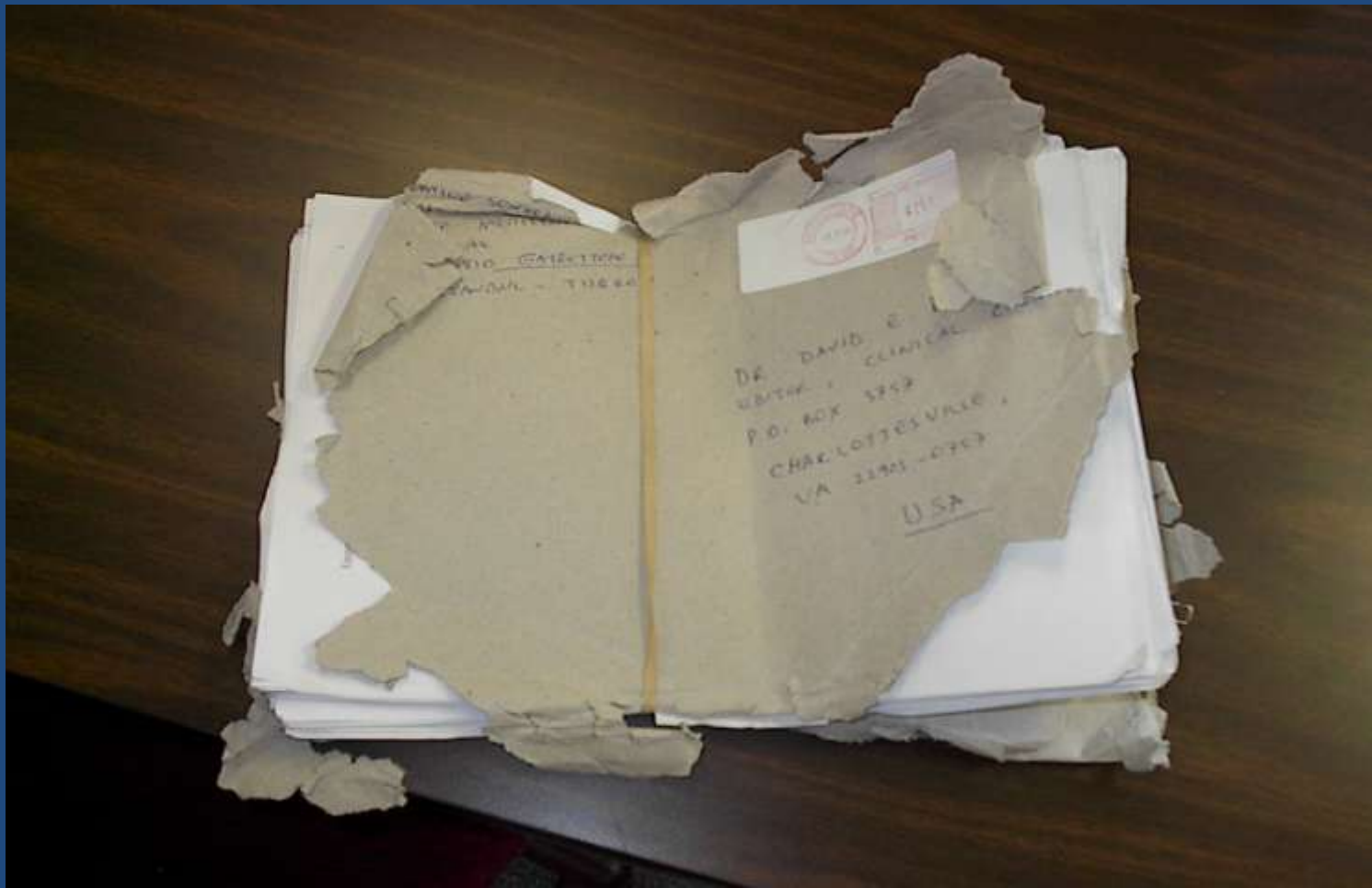
-- J. Stanton King, PhD

Human nature...

Cover letter:

Dear Sir or Madman,

Precious Jewel Arrives (Turn of the Century)



Methods Section:

Serum samples were collected from patients enrolled in a clinical trial and stored in a – 20 °C freezer.

Methods Section:

Monitoring of a work environment is performed by analyzing urine-exposed workers.

Methods Section:

Data were registered for the...traditional tests: B-glucose, C-reactive protein, ESR, urine sticks, differentiation of blood cells, wind-chill factor, mononucleosis, protrombin complex.

Results Section:

...72% of the patients had
chronic lactic acidemia ...

The danger of spell-checking words
like thrombocytes...

Results

“...blood cells [are] Erythrocytes, Leucocytes, and Trombonists.”

Reviewers' Comments

There are many misspelled works
and typographical mistakes.

Reviewer's Comment:

The author should use a paired t-test.

Reviewer's Comment:

The author should use a paired t-test.

Author's Response:

We have used both paired and unpaired t-test.

Note from an author to the copyeditor

Dr **Burns** should be credited for an excellent editing work.



For a real history,
see timeline
by Bob Rej
in Clin Chem



What Are the Future Directions for Clinical Chemistry and Laboratory Medicine?

What Are Future Directions?

“Predictions are difficult, especially about the future.”

What Are Future Directions?

Predictions are difficult, especially about the future.

- Niels Bohr (physics)

Some notable predictions:

“Radio has no future.” (Lord Kelvin, ca. 1897)

“I think there is a world market for maybe five computers.”
(Th. Watson, Chmn IBM, 1943)

“In the future, computers may weigh no more than 1.5 tonnes.” (Popular mechanics, 1949)

“No one will need more than 637 kb of memory for a personal computer.” (Bill Gates, 1981)

Directions in Clinical Chemistry and Laboratory Medicine

Opportunities are many.

A few:

- New Opportunities To Improve Health
- Increased Demand for Testing
- New Technologies

New Opportunities To Improve Health

- Epigenetics
- Genomics
- Tailored selection of anti-tumor drugs
- Proteomics, metabolomics, and other –omics
- Global Health Initiatives
- Comparative Effectiveness Research
- Electronic medical records
- Communications technology

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- Electronic medical records
- **Communications technology**

Communication

- As laboratories grew, contact with clinicians suffered.
- Clinicians are busy.
- Real and perceived laboratory errors frequently are not reported by clinicians.
- Information systems must be harnessed to help us.

Communication

- No current electronic medical record (EMR) system in US allows seamless communication from physician to the laboratory.

Communication

- Communication is needed to allow clinicians to:
 - **Easily** request checking of suspect results
 - **Easily and quickly** alert laboratory to erroneous results
 - **Easily** enlist aid of laboratory professionals in test interpretation and follow-up testing
- A communications standard is under development.

Directions

Opportunities are many. A few:

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Increased Demand for Clinical Testing

- 53 Low-income countries to become middle-income by 2020.
- Pandemic of noncommunicable disease
- Screening to identify early disease
- Ageing populations
- Increased middle class (US intelligence security assessment)
- Globalization continuing
- US: “Affordable Care Act” will pay for testing

Directions

Opportunities are many. A few:

- New Opportunities To Improve Health
- Increased Demand for Testing
- **New Technologies**

New Tools for Testing

- Microarrays
- Time-of-flight Mass Spectrometry
- Automation
- Hand-held disposable electronics
- Monitoring via smart phone
- Artificial pancreas in your smart phone
- Fast, powerful, and cheap computing and data storage
- Next-generation sequencing

Sequencing

- **Pyrosequencing** (Roche 454) Sequencing by synthesis
- **Sequencing by Oligonucleotide Ligation and Detection** (SOLiD, Applied Biosystems)
- **Cluster amplification** (Genome Analyzer, Illumina)
- **Single-molecule sequencing** (HeliScope, Helicos BioSciences)



Directions

- New Opportunities To Improve Health
- Increased Demand for Testing
- New Technologies

Thoughts on Predicting the Future

We, or at least I, can have no conception of human life and human thought in a hundred years or fifty years. Perhaps my greatest wisdom is that I do not know. The sad ones are those who waste their energy in trying to hold it back, for they can only feel bitterness in loss and no joy in gain.

John Steinbeck,

1961, Travels with Charley

There is a tide in the affairs of men.
Which, taken at the flood, leads on to fortune;
Omitted, all the voyage of their life
Is bound in shallows and in miseries.
On such a full sea are we now afloat,
And we must take the current when it serves,
Or lose our ventures.

Julius Caesar Act 4, scene 3.

Thank You.

