University Inventions that Changed the World

(or changed something at least)

Dr. Ashley J. Stevens
Lecturer
Strategy and Innovation Department
School of Management

Boston University

Trivia

- Who is the most famous Professor who's ever been a member of BU's faculty?

Clues:

- Not known for his scientific discoveries or learned writings
- Applied a 50 year old scientific discovery to meet unmet consumer needs
- Couldn't interest the leading company in his industry to take up his ideas
- Founded his own company, with his father-in-law, to commercialize

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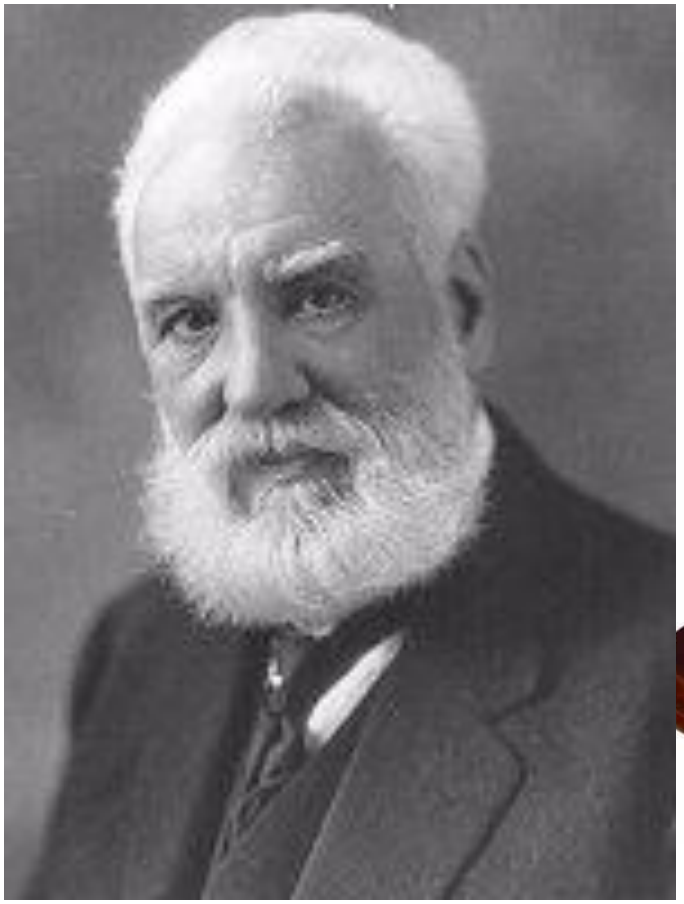

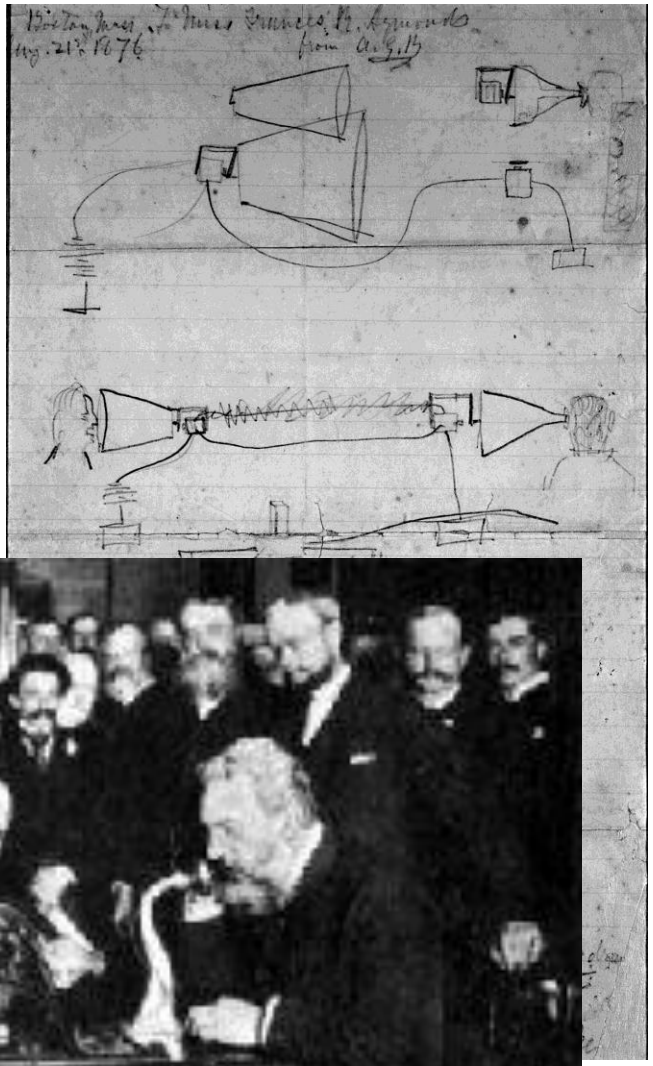

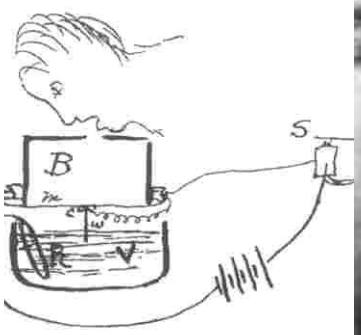
B
S
V

Alexander Graham Bell

1873 Appointed Professor of Vocal Physiology and Elocution at Boston University

1874 Started experimenting with electricity; worked on a harmonic multiple telegraph system

1875 Dean Monroe made one year salary advance

1876 Patent prepared January 15 - February 13; filed morning of February 14; Elisha Grey filed caveat in afternoon

Interference declared February 19; dissolved February 25

US Patent 174,465 issued March 7;

"Mr. Watson -- come here -- I want you" March 10, 1876

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No. 174,465

The United States of America

TO ALL TO WHOM THESE PRESENTS SHALL COME:

Whereas Alexander Graham Bell, of Salem, Massachusetts

has presented to the Commissioner of Patents a petition praying for the grant of LETTERS PATENT for an alleged new and useful

Improvement in Telegraphy

a description of which invention is contained in the Specification of which a copy is hereunto annexed and made a part hereof, and has complied with the various requirements of Law in such cases made and provided, and

Whereas upon due examination made the said Claimant is adjudged to be justly entitled to a Patent under the Law;

Now therefore these **LETTERS PATENT** are to grant unto the said Alexander Graham Bell, his heirs or assigns for the term of seventeen years from the Seventh day of March one thousand eight hundred and seventy six, the exclusive right to make, use and vend the said invention throughout the United States and the Territories thereof.

In testimony whereof I have hereunto set my hand and caused the seal of the Patent Office to be affixed at the City of Washington this seventh day of March in the year of our Lord one thousand eight hundred and seventy six, and of the Independence of the United States of America the one hundredth.

Countersigned and Sealed

Secretary of the Interior

Commissioner of Patents

2 Sheets—Sheet 1.

A. G. BELL.

TELEGRAPHY.

No. 174,465. Patented March 7, 1876.

Fig. 1

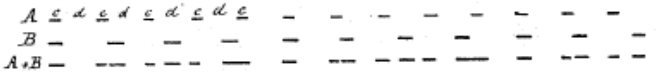


Fig. 2.

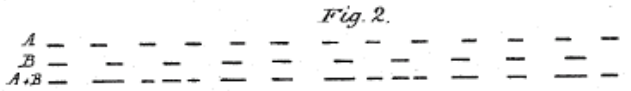


Fig. 3.

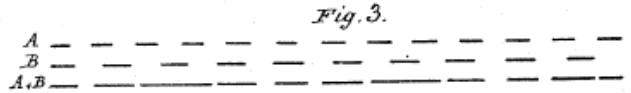


Fig. 4.

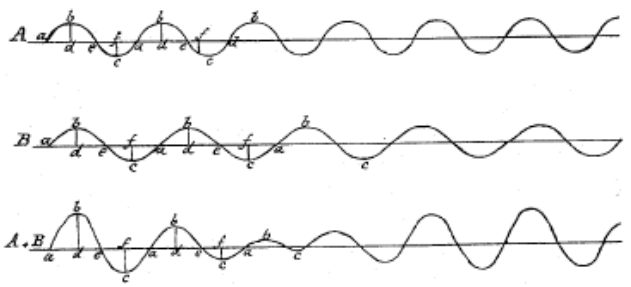
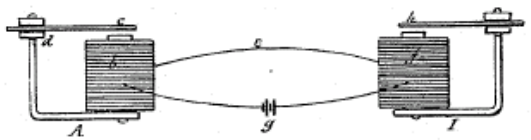


Fig. 5.



Witnesses

Ewell A. Brock.

W. J. Hutchinson

Inventor:

A. Graham Bell

by Pollok & Bailey

And Now, the Rest of the Story……

- Spent the next 17 years defending the patents
- Over 600 lawsuits 1876 - 93
- Defended by Frederick Fish
- Only finally confirmed by 4 – 3 vote of the Supreme Court in 1887

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AMERICAN TELEPHONE AND TELEGRAPH COMPANY

The Aftermath

- Sold his Bell System stock fairly early
- Was involved in the early days of the airplane
  - Aligned with Curtiss in the Curtiss-Wright Brothers battle

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My Selections

Golden Oldies

- The Telephone
- Penicillin
- Insulin
- The Pill

What Have You Done for Me Recently

- Genetic Engineering
- "Axel"
- Google
- The Web Browser/Email
- Akamai

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Fall in Two Areas

- Health care
- Communications – specifically the Web

BOSTON UNIVERSITY

Insulin

- Life saving medication
- Created/transformed three major pharmaceuticals


INSULI
50 Units—5 C.C.
10 Units per C.C.
CONNAUGHT LABORATORIES
UNIVERSITY OF TORONTO


ALFR
NOBEL


HYPODERM
ILETIN
20....UNITS IN 5 C.C.
Iletin is obtained from pancreas and is the active principle from the islet tissue regulating sugar metabolism.
This solution should be kept in a refrigerator.
Lot No. 65355 721688 Date Distributed. 10 16 1922
ELI LILLY & COMPANY, INDIANAPOLIS, U. S. A.

Three Inventors

Two M.D.’s

- Fred Banting
- J. J. R. Macleod

Two Ph.D.’s

- Charles Best
- James Collip

HAVE THEY ROBBED DIABETES OF ITS TERRORS?

shown in these pictures are the four Toronto medical men on the University staff who figure most prominently in the discovery of a pancreatic extract to be used in the clinical treatment of diabetes in human beings. This is one of the most important medical discoveries of modern research, whose possibilities as an ultimate cure of this dread disease are very encouraging. It may be gathered from the announcement to-day of the success of the extract on seven human patients at the Toronto General Hospital since January this year. Dr. F. G. Banting on the upper left, a young man of 30, a graduate from Toronto University in 1916, brought his hypothesis at the basis of the experiments with him from London, Ontario, last May. Associated with him in all the experimental work has been a younger man still, Dr. C. H. Best, only 23 years of age, on the upper right, a nephew of Mrs. Prof. Hall-Jones, of Westville College and a son of Dr. (d. H. Best, of Maine. Dr. Best on account of the promise of his work, was chosen by Prof. J. J. R. Macleod, associate Dean of Medicine at the University, and one of the most eminent authorities on diabetic research, to assist Dr. Banting in his experiments. Dr. J. B. Collip, on the lower left, professor of bio-chemistry at the University of Alberta, on leave of absence this year as assistant-professor of pathological chemistry at Toronto, a graduate of 1912, has greatly facilitated the work in refining and concentrating the extract from ox pancreas that [illegible] used on human beings for the first time in the laboratory at the General Hospital.

Star Weekly

Source: **The Discovery of Insulin, Michael Bliss, University of Chicago Press, 1982**

Discoverer

- M.D.'s shared the 1923 Nobel Prize
- Each shared their part of the prize with their Ph.D. partner
- M.D.'s not included on original patent applications
  - Patents considered to be a violation of the Hippocratic Oath
- Banting added towards end of prosecution because of need to have correct inventorship
  - University agreed to defend him against accusations of Hippocratic Oath violation
- US Patent 1,469,994 issued January 23, 1923

BOSTON UNIVERSITY

Diabetes

- Childhood death sentence
- Lives prolonged by starvation
- Known to be produced by pancreas
- A number of investigators had tried to isolate without success
- In 1921, Fred Banting had idea for ligating the pancreatic ducts of dogs to isolate the internal secretions
- Approached Professor MacLeod at U. of Toronto
  - Skeptical
  - Gave them resources over summer 1921
  - Worked; successfully lowered blood glucose of diabetic dogs

BOSTON UNIVERSITY

Initial Development

- Initial paper published February 1922
- First scale up was to fetal calf pancreases
- Learned to extract insulin from fetal calf pancreases with alcohol
- Then tried extracting adult bovine pancreases
- First human test December 21, 1921
  - Leonard Thompson
  - 14 years old
  - 65 lbs
- Blood sugar only dropped from 0.440 to 0.320
- Improved purification process – precipitated insulin out

BOSTON UNIVERSITY

Initial Development

- Second test on Leonard Thompson January 23, 1922
- Blood sugar dropped from 0.520 to 0.120
- Full clinical scale up
- Needed corporate help to scale up

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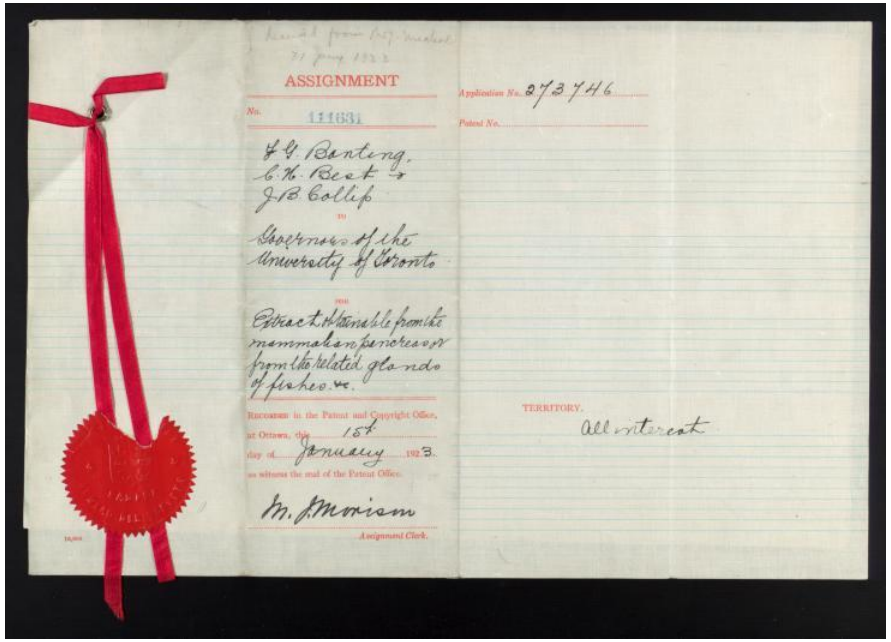
University of Toronto

- E.C. Kendall, Mayo Clinic, discoverer of thyroxin, recommended patenting
  - Motive was to retain control over the process and exploitation
  - Prevent anyone else obtaining a patent


ASSIGNMENT

No. 111631

Application No. 273746

Patent No.

F.G. Banting,
C.H. Best &
J.B. Collip

to

Governors of the University of Toronto

Extract of Insulin from the mammalian pancreas or from the related glands of fishes &c.

Territory. All interest

Recorded in the Patent and Copyright Office, at Ottawa, this 15th day of January 1923.

as witness the seal of the Patent Office.

M. J. Morisset

Assignment Clerk.

Patented Oct. 9, 1923. 1,469,994

UNITED STATES PATENT OFFICE.

FREDERICK G. BANTING AND CHARLES HERBERT BEST, OF TORONTO, ONTARIO, AND JAMES BERTRAM COLLIP, OF EDMONTON, ALBERTA, CANADA, ASSIGNORS TO THE GOVERNORS OF THE UNIVERSITY OF TORONTO, OF TORONTO, ONTARIO, CANADA.

EXTRACT OBTAINABLE FROM THE MAMMALIAN PANCREAS OR FROM THE RELATED GLANDS IN FISHES, USEFUL IN THE TREATMENT OF DIABETES MELLITUS, AND A METHOD OF PREPARING IT.

No Drawing. Application filed January 12, 1923. Serial No. 612,158.

To all whom it may concern:

Be it known that we, FREDERICK G. BANTING and CHARLES HERBERT BEST, of the city of Toronto, in the county of York and Province of Ontario, Dominion of Canada, and JAMES BERTRAM COLLIP, formerly of the said city of Toronto, and now of the University of Alberta, in the city of Edmonton, in the Province of Alberta, Dominion of Canada, British subjects, have invented an extract obtainable from the mammalian pancreas or from the related glands of fishes, useful in the treatment of diabetes mellitus, and a method of preparing it; and we hereby declare that the following is a full, clear, and exact description of the same, this application being a substitution in part of the application filed by the said JAMES BERTRAM COLLIP and CHARLES HERBERT BEST on the 22d day of May, 1922, Serial No. 562,835.

Previous investigators suggested that the ductless portion of such glands as the mammalian pancreas and the pancreas of cartilaginous fishes, known as the isles of Langerhans, and related glands (principal islets) of bony fishes contains an internal secretion or hormone capable of alleviating diabetic symptoms in patients and in laboratory animals; and other conducted experiments in which diabetic patients and diabetic laboratory animals were given extracts containing this secretion or hormone.

The results of these experiments were not considered sufficiently satisfactory to justify the continued use of the extracts in the treatment of diabetes in man because of the presence in the extracts of toxic substances, and apparently no definite progress was made towards the preparation of an extract sufficiently pure to be safely administered to human patients until these experiments were continued by us. From our knowledge of the results in the early experiments we concluded that the presence of toxic substances in the extract caused local irritation followed by general reactions unrelated to the physiological and therapeutic effects of the hormone, and these conclusions were confirmed by our early clinical observations. We, therefore, deemed it advisable before further clinical trials were undertaken to prepare the extract containing the secretion or hormone in practically pure form and to devise suitable means for obtaining the maximum yield of it.

This was done by extracting the internal secretion or hormone from the fresh pancreas of mammalia, or, from the fresh pancreas of cartilaginous fishes, or, from fresh related glands, (principal islets), of bony fishes, with a solvent capable of preserving the activity of the internal secretion or hormone and then separating it practically free from injurious substances including inert associated gland tissue, proteins, proteolytic enzymes, salts and lipoids.

The following are steps we employed in several methods for obtaining a practically pure extract from the fresh pancreas of mammalia:

(1) Separation of the internal secretion or hormone from the fresh pancreas by extraction with solvents such as ethyl alcohol, methyl alcohol, methylated spirits, and acetone, or any mixture of these, which are capable of preserving the activity of this internal secretion or hormone by not destroying it and by largely preventing or inhibiting the deleterious action on it of such proteolytic enzymes as trypsin, erepsin, and the proteases, and of other catalysts present, followed by filtration for the removal of the inert associated gland tissue.

(2) Removal of the major part of the proteins by some suitable method of precipitation. For this purpose alcohol, colloidal iron, precipitation at isolectric point by the use of dilute acid or alkali, or heating to a suitable temperature, may be used.

(3) Concentration of the extracted filtered solution, either before or after the removal of the proteins, as by distillation in vacuo, or evaporation in a dry air current.

(4) Removal of the lipoids after concentration either by mechanical separation or by chemical extraction with solvents such as ether, or toluol.

(5) Removal of the salts and a large part of the remaining impurities by precipitation with alcohol.

(6) Precipitation of the internal secretion or hormone with adherent substances

Claim Number 1

administered.

Having thus fully described our invention what we claim as new and desire to secure by Letters Patent is

1. A substance prepared from fresh pancreatic or related glands containing in concentrated form the extractive from the ductless portion of the glands sufficiently free from injurious substances for repeated administration and having the physiological characteristics of causing a reduction of blood sugar useful for the treatment of diabetes mellitus.

Commercialization

- Transformed/Created three drug companies:
  - Eli Lilly
  - Connaught Laboratories
  - Novo Nordisk

BOSTON UNIVERSITY

Eli Lilly

- Founded 1876
- Ethical pharmaceuticals only – no “patent medicines”
- 1,100 employees, $5 million revenues, run by J.K. Lilly, son of founder
- George Clowes hired as special research chemist in 1919; Director of Research 1920
- Learned of work through academic contacts
- Attended first public presentation of work – New Haven, December 30, 1921
  - Immediately proposed collaboration

BOSTON UNIVERSITY

Eli Lilly

- 1 year exclusive INDENTURE signed May 30, 1922
- Territory limited to US, Central and South America
- Lilly supplied free initially; in January 1923 sold at cost – 5¢/dose – for testing period
- Improvements shared back to Toronto, patent pool outside the US
- Lilly established brand name “Iletin”
- Sales >$1 million in first year
- Transformed company into a major pharmaceutical company

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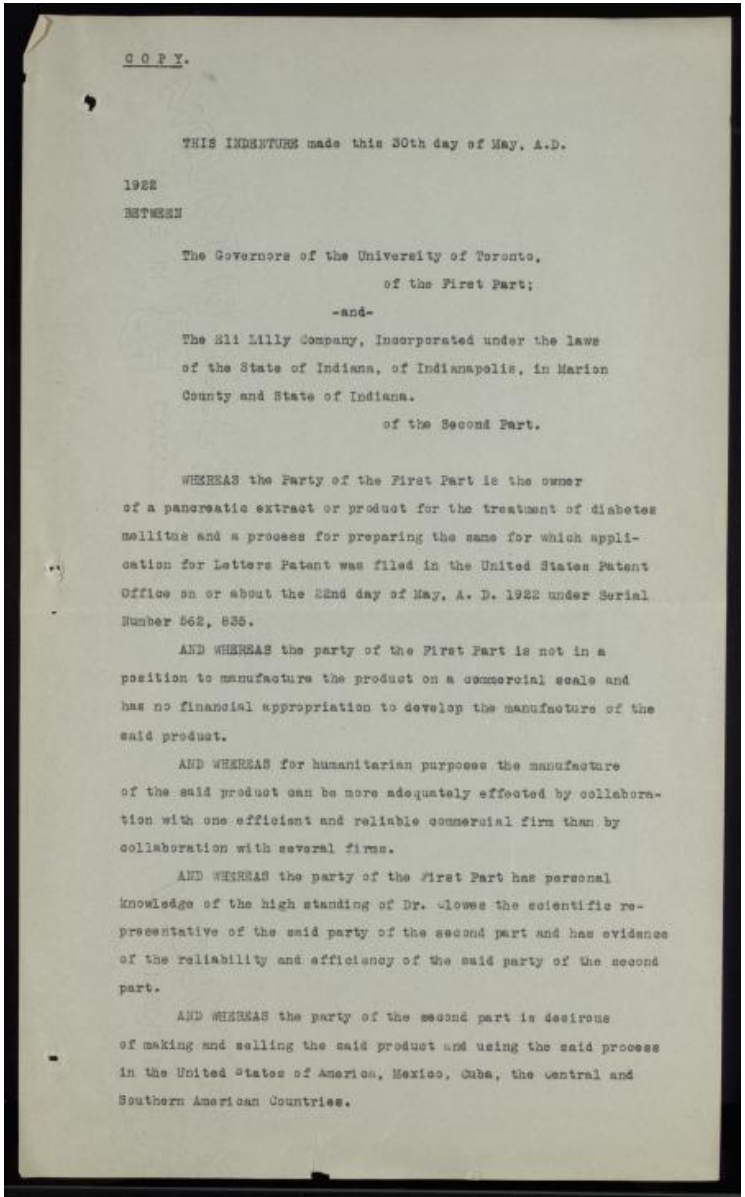
The first 5% royalty for an academic license



COPY.

THIS INDENTURE made this 30th day of May, A.D.

1922

BETWEEN

The Governors of the University of Toronto,
of the First Part;

-and-

The Eli Lilly Company, Incorporated under the laws of the State of Indiana, of Indianapolis, in Marion County and State of Indiana.
of the Second Part.

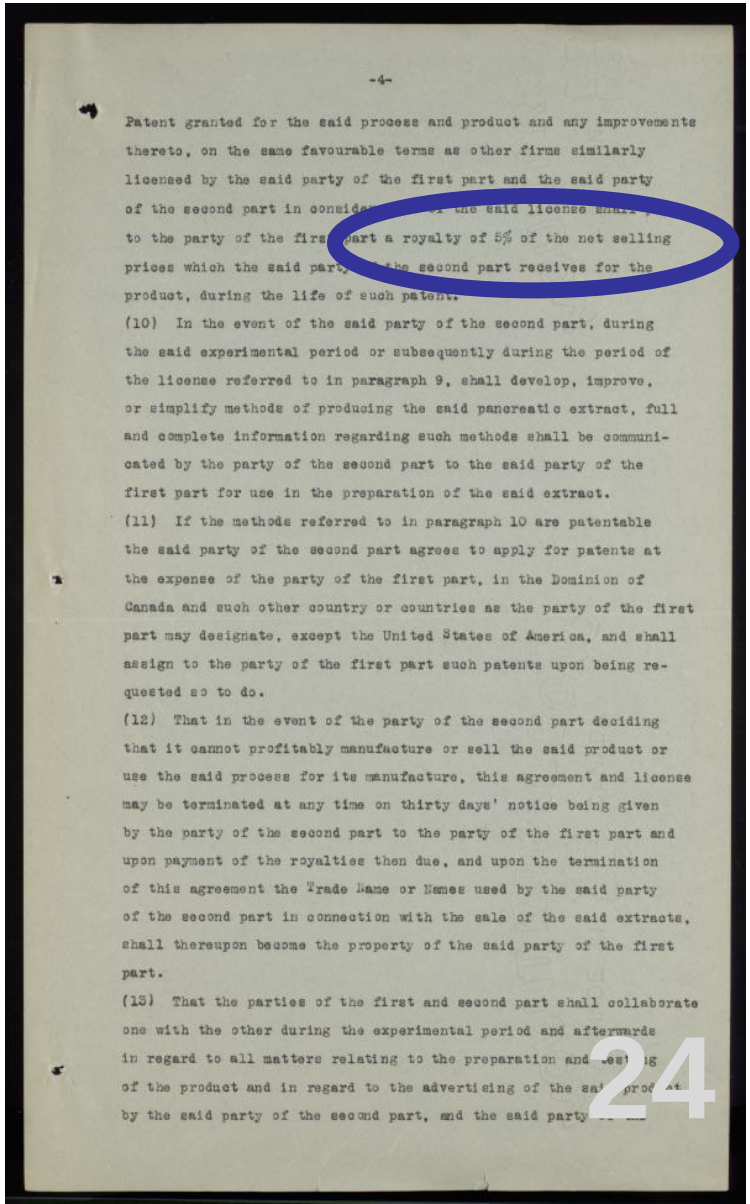
WHEREAS the Party of the First Part is the owner of a pancreatic extract or product for the treatment of diabetes mellitus and a process for preparing the same for which application for Letters Patent was filed in the United States Patent Office on or about the 22nd day of May, A. D. 1922 under Serial Number 562, 835.

AND WHEREAS the party of the First Part is not in a position to manufacture the product on a commercial scale and has no financial appropriation to develop the manufacture of the said product.

AND WHEREAS for humanitarian purposes the manufacture of the said product can be more adequately effected by collaboration with one efficient and reliable commercial firm than by collaboration with several firms.

AND WHEREAS the party of the First Part has personal knowledge of the high standing of Dr. Clowes the scientific representative of the said party of the second part and has evidence of the reliability and efficiency of the said party of the second part.

AND WHEREAS the party of the second part is desirous of making and selling the said product and using the said process in the United States of America, Mexico, Cuba, the Central and Southern American Countries.



-4-

Patent granted for the said process and product and any improvements thereto, on the same favourable terms as other firms similarly licensed by the said party of the first part and the said party of the second part in consider[illegible] the said license shall [illegible] to the party of the first part a royalty of 5% of the net selling prices which the said party of the second part receives for the product, during the life of such patent.

(10) In the event of the said party of the second part, during the said experimental period or subsequently during the period of the license referred to in paragraph 9, shall develop, improve, or simplify methods of producing the said pancreatic extract, full and complete information regarding such methods shall be communicated by the party of the second part to the said party of the first part for use in the preparation of the said extract.

(11) If the methods referred to in paragraph 10 are patentable the said party of the second part agrees to apply for patents at the expense of the party of the first part, in the Dominion of Canada and such other country or countries as the party of the first part may designate, except the United States of America, and shall assign to the party of the first part such patents upon being requested so to do.

(12) That in the event of the party of the second part deciding that it cannot profitably manufacture or sell the said product or use the said process for its manufacture, this agreement and license may be terminated at any time on thirty days' notice being given by the party of the second part to the party of the first part and upon payment of the royalties then due, and upon the termination of this agreement the Trade Name or Names used by the said party of the second part in connection with the sale of the said extracts, shall thereupon become the property of the said party of the first part.

(13) That the parties of the first and second part shall collaborate one with the other during the experimental period and afterwards in regard to all matters relating to the preparation and [illegible] of the product and in regard to the advertising of the sai[illegible] by the said party of the second part, and the said party [illegible]

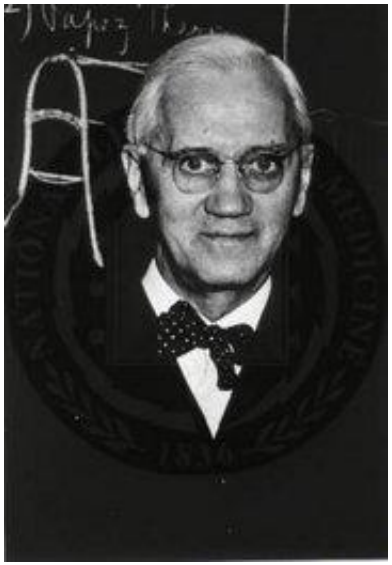
University of Toronto

- Only collected royalties in US and Canada
- Meat packers competed
  - Armour Pharmaceuticals “Insulase”
  - Digestive Ferments Company “I’Lang-Hans”
  - Philadelphia Capsule Company “Insulans”
  - Harrower Laboratories “Pan-Secretin”
- MRC strongly resisted
- Patents expired in 1960’s
- Royalties:
  - ~$180,000 per year in 1930’s
  - $8 million 1923 - 1960

BOSTON UNIVERSITY

Penicillin

- **Showed that one of the three great scourges of mankind could be beaten**
- **Showed the importance of scientists getting patents on their work**

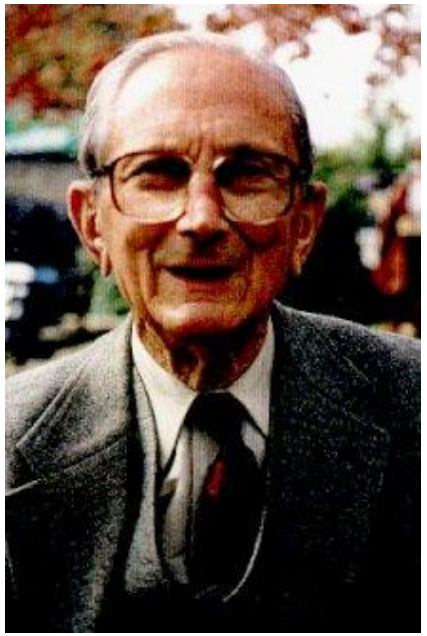


Sir Alexand

Sir Howard Florey

Norman Heatley

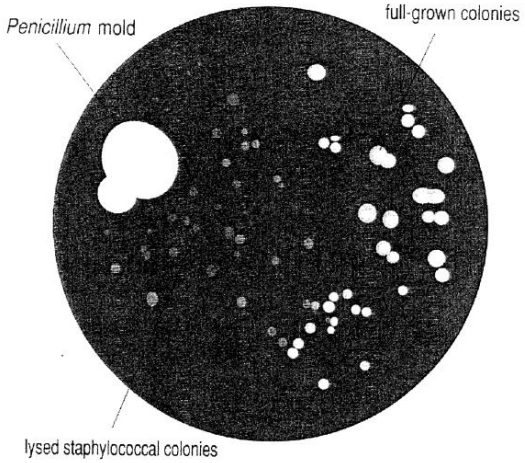
Ernst



St Mary's Hospital Medical School, London

Initial Discovery

- Alexander Fleming discovered lysozyme (from his own runny nose!) in 1921
- Discovered penicillin in 1928; thought it was another enzyme



- Showed antibacte l penicillin very unstable; never did *in vivo* experiments
- Published in *British Journal of Experimental Pathology*; ceased working on penicillin in 1932

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Penicillin notatum

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The Oxford Period – Sir William Dunn School of Pathology

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The Oxford Team

- Howard Florey was an Editor of *British Journal of Experimental Pathology*
- Appointed Professor of Pathology at Oxford in 1935
- Studied lysozyme; showed it was an enzyme
- In 1938, Ernst Chain, biochemist, discovered Fleming's paper on penicillin; thought it was an enzyme similar to lysozyme
- Another lab had a culture of *P. notatum*
- Started growing in September 1939
- Funding from MRC and Rockefeller Foundation
  - MRC given £1,000,000 for 5 years in 1934!
  - Initial grant to Florey £25!

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Initial Development of Penicillin

- In 1940, Heatley developed methods to extract based on acidic nature of penicillin
  - From broth into ether
  - From ether into alkaline water
- Scaled up; second generation version cost £5!
- First mouse tests showed no toxicity and *in vivo* stability in March 1940
- First demonstration of protection against *Streprococcus haemolyticus* May 25, 1940
- Initial article in *Lancet* on August 25, 1940; got US attention
  - Columbia, Pfizer, E.R. Squibb
- First human trials in January 1941 at Radcliffe Infirmary; pyrogenic response

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Clinical Development

- First treatment February 1941
  - Albert Alexander; policeman who scratched his nose on a rose
  - Immediate improvement
  - Collected urine and re-extracted penicillin
  - Relapsed; no further penicillin – second patient being treated
  - Died
- Couldn't get any company to help with scale up; decided to get US help in June 1941
- USDA NRRL in Peoria had developed submerged fungal fermentation using corn steep liquor for citric acid production in 1935
- Developed method; Merck, Squib and Pfizer initial collaborators

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Into Production

- War Production Board financed 21 US companies to produce it
- First 5 months of 1943 produced 400 million units
  - Enough to treat 180 cases
- Last seven months of 1943, 20.5 billion units
- By D-Day, 100 billion units a month
  - 40,000 cases
- Pfizer the big winner
  - 50% market share
- Because of competition and scale, price dropped from $200 to $6/million units,

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Patent Issues

- British tradition of non-commercialization
- Chain understood power and importance of patents
- Edward Mellanby, secretary of the MRC, forbade it:
  - ".....told Chain that if he persisted in his 'money grubbing' he would have no scientific future in Britain...."
  - "….cornering of penicillin was to be avoided at all costs…."
- Andrew Moyer, USDA Peoria
  - Not allowed to get US patents
  - Got UK patents in his own name
  - UK had to pay him royalties

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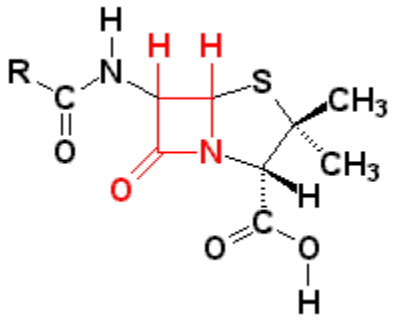
Patent Issues

- UK probably would have had problems if it had tried
- Only 2 types of patents then
  - Composition
    - Fleming 1929 paper prior art
    - Penicillin F (UK) vs. Penicillin G (US)
  - Production method
  - No method of treating patents then
- National Research and Development Corporation set up to patent British academic inventions
- Edward Abraham discovered cephalosporins
  - Comprehensively patented
  - £80 million in royalties

BOSTON UNIVERSITY

Recognition

- Fleming and Florey knighted in June 1944
- 1945 Nobel Prize (£8,500) shared equally
  - Fleming
  - Florey
  - Chain
- Dorothy Hodgkin received 1964 Nobel prize for determining the structure by X-ray crystallography



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The Pill

- **Transformed human sexuality**
- **Failure to utilize the patent system ultimately led to the demise of the institution where it was developed**

A Story of Two Strong Women and Two Strong Men

Margaret Sanger

The Driving Force

Katharine McCormick

The Financier

Gregory Pincus

The Reproductive Physiologist

John Rock

The Clinician

Katharine McCormick

- Married Stanley McCormick
  - Youngest son of Cyrus McCormick, inventor of the reaper and founder of International Harvester
- Developed schizophrenia; institutionalized
- Family lawyers limited her control of family assets
- Died 1947
  - Katharine was 71
- 5 year court battle to get control of assets -- 1952

BOSTON UNIVERSITY

Margaret Sanger

- Suffragette
- Pioneered birth control, despite Comstock Laws making it illegal
- Met Katharine McCormick in 1917
- Founded Planned Parenthood
  - Started helping Sanger's birth control efforts in 1927
  - In 1952 had funds to really help
- Planned Parenthood had put modest funding into Pincus work
- McCormick agreed to fund the entire effort
  - $2 million over the entire timeframe

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Gregory Pincus

- Harvard reproductive physiologist
- A Jew
- Became infamous for first artificial insemination of a rabbit
- Denied tenure
- Founded Worcester Foundation for Experimental Biology
  - One of the first translational research institutes
  - Hormone research becoming important
  - Reproduced 1933 work of Makepeace at Penn showing progesterone halted ovulation in rabbits
  - Worked but needed enormous doses, by injection

BOSTON UNIVERSITY

John Rock

- Harvard gynecologist – Boston City Hospital
- A Catholic
- Working with synthetic progesterones plus estrogen to treat infertility
  - Stop ovulation for two years, hoped for “bounce back”
  - Already treating women at BCH
  - Worked – 13 out of eighty
- Met Pincus in 1952
- Agreed to collaborate
- Massachusetts was last state with Comstock Laws
  - Shielded behind “Menstrual Irregularity”

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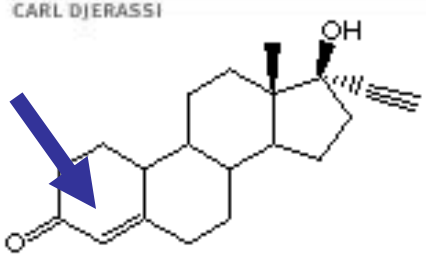
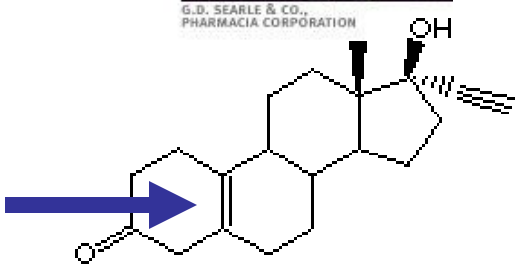
The Breakthrough

- Had to have a more potent, preferably oral, version
- Contacted all pharmaceutical and chemical companies looking for novel compounds
- Received two almost identical samples:
  - Carl Djerrasi, Syntex
  - Frank Colton, G.D. Searle



Norethindrone



Norethynodrel

BOSTON UNIVERSITY

The Fatal Blunder

" Both claimed that these particular samples, taken as menstrual-cycle regulators, were *most effective when taken orally.* Neither sample was accompanied by the faintest hint that anyone had thought of it as contraceptive. But unless Pincus was making a huge mistake, *the chemistry of the Pill he sought was already invented.* "

The Pill
Bernard Asbell

BOSTON UNIVERSITY

Clinical Development

- Used the Searle version
  - Later found small estrogen content was highly beneficial
- 50 patient trial at BCH 1954 -55
  - None ovulated
  - Still fertility oriented – not contraceptive
- Announced at International Planned Parenthood conference in Tokyo, October 1955
  - Implications almost overlooked
  - Implications described in closing session
- Large scale clinical trial through Puerto Rico Public Health Service system of 67 Birth Control Clinics
  - Led by Dr. Edris Rice-Wray
- Expanded to Haiti and Mexico
  - 20,000 woman tested

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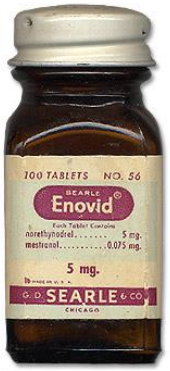
Market Launch

- Dosage fine tuned
- Failure rate 1.7 per 100 woman years
- Initial approvals by Parke-Davis and G.D. Searle for menstrual irregularities in 1957
- Searle applied for approval for Enovid contraceptive use in 1959



COURTESY G.D. SEARLE & CO. / PHARMACIA CORPORATION

COURTESY OF THE NATIONAL MUSEUM OF AMERICAN HISTORY
BEHRING CENTER, SMITHSONIAN INSTITUTION

COURTESY OF THE NATIONAL MUSEUM OF AMERICAN HISTORY
BEHRING CENTER, SMITHSONIAN INSTITUTION

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Worcester Foundation

- Merged with University of Massachusetts Medical School in 1997

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Genetic Engineering

- **Transformed the pharmaceutical industry**
- **Led to an enormous number of revolutionary medicines**
- **The first US academic blockbuster income generator**

Stan Cohen **Herb Boyer**

Stanford

UCSF

BOSTON UNIVERSITY

The Precursors

- Francis Crick, Maurice Wilkins, James Watson and Rosalind Franklin discovered structure of DNA in 1953;
- Paul Berg showed gene splicing in viruses in 1972
- Boyer worked on restriction enzymes
  - From bacteria, cut DNA
  - Sticky ends – would join to form a new DNA molecule
- Cohen worked on plasmids
  - Small circular pieces of DNA
  - Naturally transmitted from one bacterium to another
  - In 1970 transferred plasmid *pSC*101 (tetracycline resistance) into *E. coli*

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The Seminal Collaboration

- Met at a conference in Hawaii in 1972; agreed over corned beef sandwiches to collaborate
- Found that *Eco* RI, would cut *pSC101* at a single site.
- Introduced gene for kanamycin resistance
- Introduced engineered plasmid into *E. coli*
- Resultant *E. coli* was resistant to tetracycline and kanamycin
- Introduced genes from toad *Xenopus laevis* into *E. coli*, showing foreign genes would work
- Presented at Gordon Conference
- Never got Nobel Prize – Paul Berg got half Chemistry Prize for work on viruses in 1980
  - Sanger and Gilbert shared other half for sequencing work

United States Patent 4,237,224

- Cohen , et al.
- December 2, 1980
- Assigned to Stanford
  - Inter-Institutional Agreement gives Stanford 57.5% and UCSF 42.5%
- Process for producing biologically functional molecular chimeras

BOSTON UNIVERSITY

Inter-Institutional Agreement gives Stanford 57.5% and UCSF 42.5%

United States Patent [19]

Cohen et al.

[11] **4,237,224**

[45] **Dec. 2, 1980**

[54] **PROCESS FOR PRODUCING BIOLOGICALLY FUNCTIONAL MOLECULAR CHIMERAS**

[75] Inventors: **Stanley N. Cohen**, Portola Valley; **Herbert W. Boyer**, Mill Valley, both of Calif.

[73] Assignee: **Board of Trustees of the Leland Stanford Jr. University**, Stanford, Calif.

[21] Appl. No.: **1,021**

[22] Filed: **Jan. 4, 1979**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 959,288, Nov. 9, 1978, which is a continuation-in-part of Ser. No. 687,430, May 17, 1976, abandoned, which is a continuation-in-part of Ser. No. 520,691, Nov. 4, 1974.

[51] **Int. Cl.**[3] **C12P 21/00**

[52] **U.S. Cl.** ..... **435/68;** 435/172; 435/231; 435/183; 435/317; 435/849; 435/820; 435/91; 435/207; 260/112.5 S; 260/27R; 435/212

[58] **Field of Search** ..... 195/1, 28 N, 28 R, 112, 195/78, 79; 435/68, 172, 231, 183

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Chemical and Engineering News, p. 6, Sep. 11, 1978.

Primary Examiner—Alvin E. Tanenholtz
Attorney, Agent, or Firm—Bertram I. Rowland

[57] **ABSTRACT**

Method and compositions are provided for replication and expression of exogenous genes in microorganisms. Plasmids or virus DNA are cleaved to provide linear DNA having ligatable termini to which is inserted a gene having complementary termini, to provide a biologically functional replicon with a desired phenotypical property. The replicon is inserted into a microorganism cell by transformation. Isolation of the transformants provides cells for replication and expression of the DNA molecules present in the modified plasmid. The method provides a convenient and efficient way to introduce genetic capability into microorganisms for the production of nucleic acids and proteins, such as medically or commercially useful enzymes, which may have direct usefulness, or may find expression in the production of drugs, such as hormones, antibiotics, or the like, fixation of nitrogen, fermentation, utilization of specific feedstocks, or the like.

14 Claims, No Drawings

Licensing

- Neils Reimer, founder of Stanford's OTL, read about work in *NY Times*
- Adopted policy of making it easy and desirable to take a license
  - $10,000 per year, low royalty rate;
  - free to academics
- Did not exclusively license to Boyer's company, Genentech
- 400 licensees when expired on December 2, 1997
- Every genetically engineered drug used it
  - Insulin, hGH, α-interferon, β-interferon, γ-interferon, tPA, MAb's, EPO, G-CSF……..
- Total income $255 million

BOSTON UNIVERSITY

Making the Web Useful

- email and the Web Browser

- **Transformed how the world works**
- **Institution made next to nothing from it**

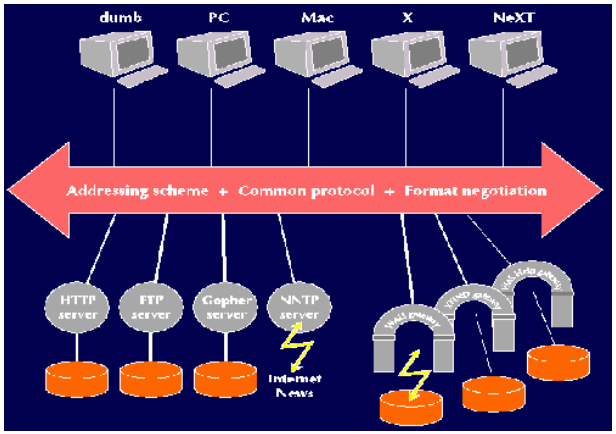
History of the Internet

- RAND Corporation study by Paul Baran for Airforce identified packet switching as basis for nuclear attack-proof command and control network
- Development initiated by ARPA in October 1962
- Objective was a redundant connectivity system
- Development initially led by Dr. J.C.R. Licklider of ARPA
- Contracted to Bolt, Beranek & Newman, Cambridge, MA in 1968
- UCLA, SRL, U. of Utah and U. of California, Santa Barbara connected in 1969; 50 kbs
- Split into ARPANet and Milnet in 1983
- ARPANET replaced by NSFNET in 1990

Individuals and the Internet

- Initially, proprietary systems
  - Email: MCIMail
  - WWW: Prodigy

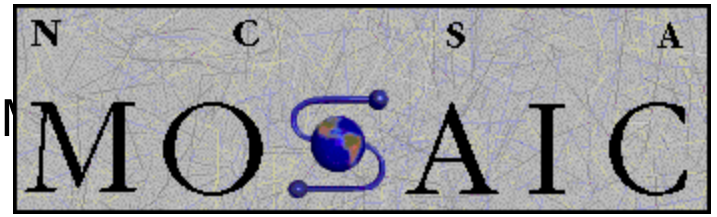
- Tim Berners-Lee and Robert Callahan developed the World Wide Web at CERN in 1989



University of Illinois Makes it Accessible and Useful

- Email — Eudora

- Web Browser — M



- National Center for Supercomputer Applications (“NCSA”)

Founding Directo
Larry Smarr

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Eudora

- Steve Dorner

- On computing staff at University of Illinois, Urbana-Champaign
- Wrote Eudora in 1988
  - V1.0 was 50,000 lines of code
  - For the Mac

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Eudora

- Name came from "Why I Live At the P.O." by Eudora Welty
  - Dorner never met her!

- Made sending and receiving email – particularly attachments – user friendly
- Licensed to Qualcomm in 1991
- Paid “More than $100,000, less than $1 million”
- Dorner got nothing – “Work for hire”
- Hired by Qualcomm and telecommuted from the 8’x8’ bomb shelter in his house

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Mosaic – the Program

- Written by Marc Andreessen
- Work for hire – NCSA owned it

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Mosaic

- First released April 1993
- 1 million downloads within first year
- Licensed to Spyglass in 1994

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Spyglass

- Founded 1990 to license NCSA technologies
- Initially scientific data management
- $3 million funding from Greylock and Venrock
- Alex Brown IPO in June 1995
- Licensed Mosaic in 1994; rewrote from scratch
- Business model – license to others
  - Per user licensing fee
- 120 licensees
  - 50¢/per user license fee
  - Gave Microsoft a flat fee (no per user) license in 1995
  - Microsoft gave away Internet Explorer
  - Spyglass sued Microsoft; settled in 1997 for $8 million
  - Microsoft ate the other 119 licensees

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Netscape

- Founded as Mosaic Communications Company
- Did not license from Spyglass
  - Objected to per user terms
- Wrote entirely new version
- Sued by U. of Illinois, claiming theft of trade secrets
  - “ But Phil, there aren’t any trade secrets to steal. This is a university ”
  - “ You are intrinsically in violation of our intellectual property because of the information in the heads of those who worked for and left the university ”
- Netscape offered some stock
- Ultimate settlement was 2 $750,000 cash payments
- If they’d taken stock for some or all, would have been worth billions

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Clark's Deal

- Initial $3 million from Clark -- $0.75/share
- First VC round -- $18 million pre
- Kleiner Perkins – John Doerr
- $17 million for 33% of company

BOSTON UNIVERSITY

Dot.com

- Spyglass IPO June 1995
  - $17
  - First day close $21
- Netscape IPO August 1995
  - Priced at $28
  - Hit $74.75
  - Market cap $2.2 billion
  - Company 15 months old

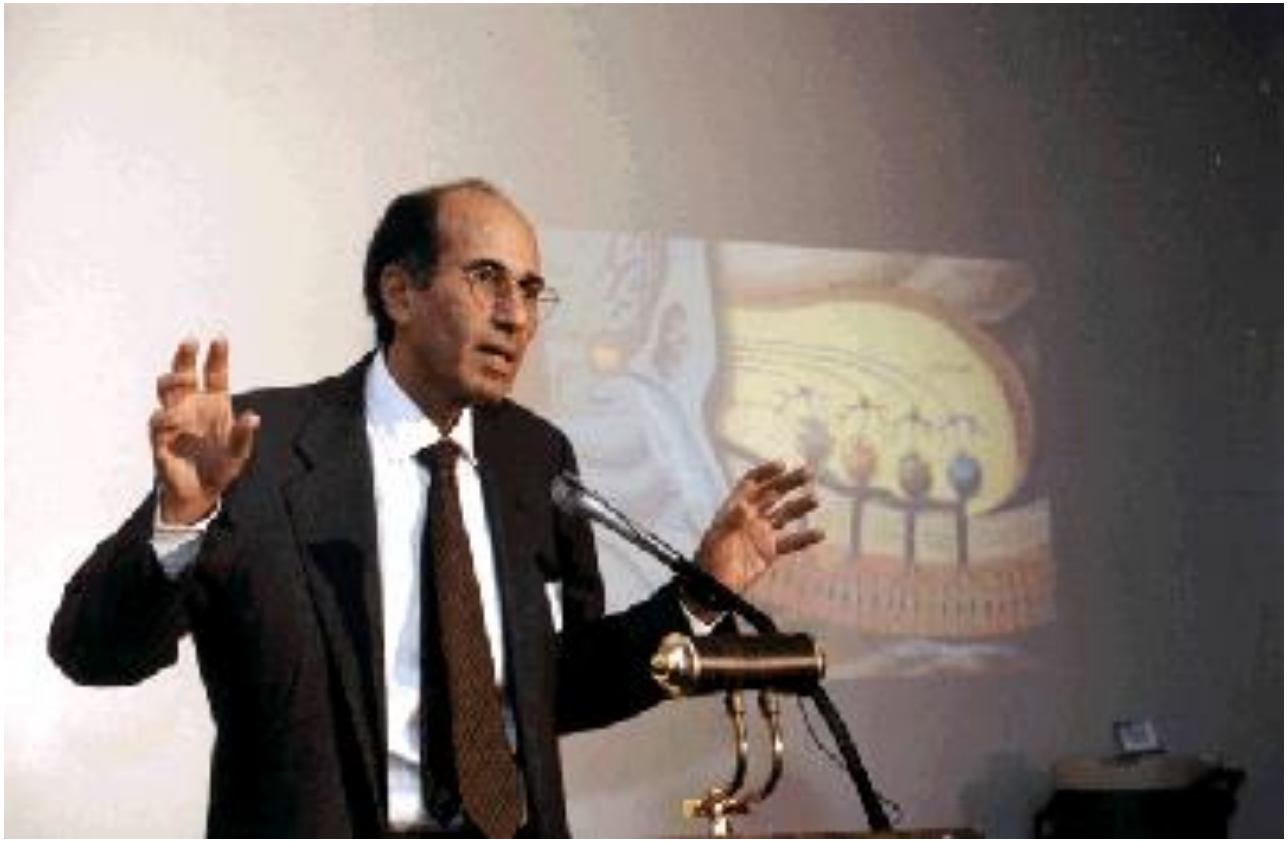
BOSTON UNIVERSITY

“Axel”

– Producing Genetically Engineered Proteins in Mammalian Cells

more royalty income than any other university patent

Richard Axel



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Co-Transformation

- Process to generate highly producing mammalian cells
- Two plasmids co-transformed into cell
  - Plasmid A with gene of interest
  - Plasmid B with selectable marker
- Select for selectable marker
  - Selects for cells with multiple copies of plasmid A
  - Multiple copies of Plasmid B as well
- Used for biopharmaceuticals that are glycosylated
  - EPO, Monoclonal antibodies, tPA, Avonex, Ceredase, etc
- Total royalty income to date $600 million
- 4th patent issued specific to CHO cells after first three expired

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United States Patent [19]

Axel et al.

[11] **4,399,216**

[45] **Aug. 16, 1983**

[54] **PROCESSES FOR INSERTING DNA INTO EUCARYOTIC CELLS AND FOR PRODUCING PROTEINACEOUS MATERIALS**

[75] Inventors: **Richard Axel**, New York; **Michael H. Wigler**, Cold Spring Harbor; **Saul J. Silverstein**, Irvington, all of N.Y.

[73] Assignee: **The Trustees of Columbia University**, New York, N.Y.

[21] Appl. No.: **124,513**

[22] Filed: **Feb. 25, 1980**

[51] **Int. Cl.**[3] **C12N 15/00**; C12N 5/00; C12P 21/00; C12Q 1/68; C12Q 1/02; C12Q 1/04

[52] **U.S. Cl.** **435/6**; 435/172; 435/240; 435/317; 435/811; 435/948; 435/29; 435/34; 435/68

[58] **Field of Search** 435/68, 172, 70, 240, 435/241, 948, 811, 6, 29, 34; 424/85, 177, 178, 180

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Primary Examiner—Esther M. Kepplinger
Attorney, Agent, or Firm—John P. White

[57] **ABSTRACT**

The present invention relates to processes for inserting DNA into eucaryotic cells, particularly DNA which includes a gene or genes coding for desired proteinaceous materials for which no selective criteria exist. The insertion of such DNA molecules is accomplished by cotransforming eucaryotic cells with such DNA together with a second DNA which corresponds to a gene coding for a selectable marker.

The invention further relates to processes for inserting into eucaryotic cells a multiplicity of DNA molecules including genes coding for desired proteinaceous materials by cotransformation with the desired genes and with amplifiable genes for a dominant selectable marker in the presence of successively higher amounts of an inhibitor. Alternatively, the insertion of multiple copies of desired genes is accomplished by transformation using DNA molecules formed by ligating a DNA molecule including the desired gene to a DNA molecule which includes an amplifiable gene coding for a dominant selectable phenotype such as a gene associated with resistance to a drug in the presence of successively higher amounts of an agent such as a drug against which the gene confers resistance so that only those eucaryotic cells into which multiple copies of the amplifiable gene have been inserted survive.

73 Claims, 2 Drawing Figures

Akamai

- the Most Valuable Ph.D. Thesis Ever

Tom Leighton

Danny Lewin

Distributed Web Caching

- Store live copies of web pages on servers round the world
- Web browsers access the copy to avoid overwhelming the home servers
- Behind the scenes part of the web

BOSTON UNIVERSITY

Technology Development

- Research started early 1995
- Provisional patent filed July 1998
- Company founded August 1998
- License with MIT signed October 1998
  - All equity -- 682,110 shares
  - Financing, technology development and sales milestones
  - Redacted!
- Series A $8.3 million November 1998 @ $7.60/share
  - Polaris, Battery
- Series B/ 15% Notes $20/$8 million March 1999 @$15.066
  - Baker Communications, Polaris, Battery
- R&D expenses $2.3 million as of July 1999

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US006108703A

United States Patent [19]

Leighton et al.

[11] **Patent Number: 6,108,703**

[45] **Date of Patent: Aug. 22, 2000**

[54] **GLOBAL HOSTING SYSTEM**

[75] Inventors: **F. Thomson Leighton**, Newtonville; **Daniel M. Lewin**, Cambridge, both of Mass.

[73] Assignee: **Massachusetts Institute of Technology**, Cambridge, Mass.

[21] Appl. No.: **09/314,863**

[22] Filed: **May 19, 1999**

Related U.S. Application Data

[60] Provisional application No. 60/092,710, Jul. 14, 1998.

[51] **Int. Cl.**[7] **G06F 13/00**

[52] **U.S. Cl.** **709/226**; 709/105; 709/219; 709/223; 709/224; 709/235

[58] **Field of Search** 707/10, 2, 104, 707/203, 500, 501, 511, 512, 513, 515; 709/200, 201, 203, 218, 219, 230, 235, 238, 245, 246, 226, 224, 105, 220; 711/118, 119, 120, 122, 126, 130, 200, 202, 216

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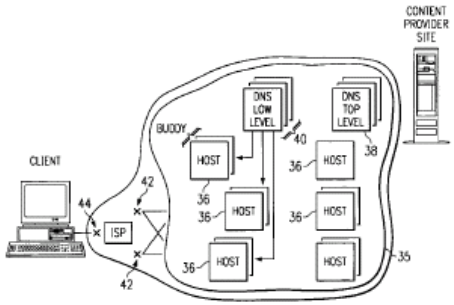
(List continued on next page.)

Primary Examiner—Dung C. Dinh
Assistant Examiner—Abdullahi E. Salad
Attorney, Agent, or Firm—David H. Judson

[57] **ABSTRACT**

The present invention is a network architecture or framework that supports hosting and content distribution on a truly global scale. The inventive framework allows a Content Provider to replicate and serve its most popular content at an unlimited number of points throughout the world. The inventive framework comprises a set of servers operating in a distributed manner. The actual content to be served is preferably supported on a set of hosting servers (sometimes referred to as ghost servers). This content comprises HTML page objects that, conventionally, are served from a Content Provider site. In accordance with the invention, however, a base HTML document portion of a Web page is served from the Content Provider's site while one or more embedded objects for the page are served from the hosting servers, preferably, those hosting servers near the client machine. By serving the base HTML document from the Content Provider's site, the Content Provider maintains control over the content.

34 Claims, 2 Drawing Sheets



IPO

- S-1 filed August 1999
- Accumulated losses $10.7 million
- Revenues (H1 1999) $403,000
- 900 Servers in 15 countries
- Representative customers:
  - Yahoo!
  - Apple Computer
  - Artisan Entertainment
  - CNN Interactive
  - Discovery Channel Online
  - Hard Rock Hotel
  - Paramount Digital Entertainment
  - Sportsline USA
  - J.Crew.com
  - CCBN
  - The Motley Fool

BOSTON UNIVERSITY

Value Created

- MIT's stake in Akamai (1998) was worth $200 million at the stock market peak (12/31/99; $312.50/share)
- 7th most valuable public company in Massachusetts in December 1999
- Stakes of Leighton and Lewin, each worth $1.85 billion at peak.
- In August 2002, Akamai voluntarily applied to delist from NASDAQ National Market
  - drillbit pricing -- $¾/share

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Akamai Stock Price History

An interesting twist – terrible publicity

- Events occurred 1999
- Reported by *WSJ* June 24, 1999
- Students worked at Akamai Technologies; signed CDA's
- Homework project assigned by Professor Frans Kaashoek would have violated CDA
- Kaashoek co- founder of SightPath, Inc., intelligent content company
- *WSJ* said Leighton accused Kaashoek of using students to gather intelligence
- Students got new assignments

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An interesting twist – terrible publicity

- MIT policy changes:
  - Students who sign CDA's will not get new assignments -- flunk course
  - Students must meet with another faculty member before being hired by faculty spin-out company

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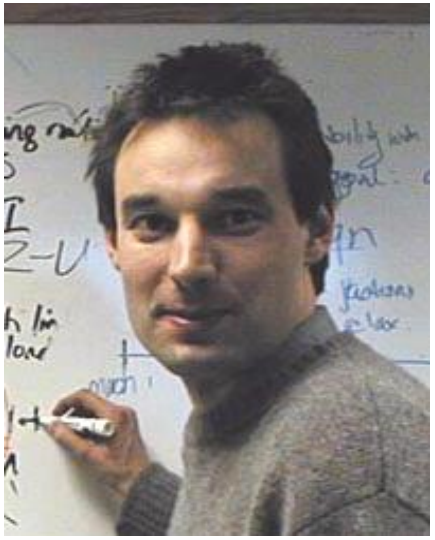
SightPath

- Founded 1998
- Funded by Greylock, Intel, and Pilot House
- Acquired for $800 million stock by CISCO Systems March 2000
- Technology completely out the back door!



US006345294B1

(12) **United States Patent**
O'Toole et al.

(10) **Patent No.: US 6,345,294 B1**
(45) **Date of Patent: Feb. 5, 2002**

(54) **METHODS AND APPARATUS FOR REMOTE CONFIGURATION OF AN APPLIANCE ON A NETWORK**

(75) Inventors: **James O'Toole**, Somerville; **M. Frans Kaashoek**, Lexington, both of MA (US)

(73) Assignee: **Cisco Technology, Inc.**, San Jose, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/294,836**

(22) Filed: **Apr. 19, 1999**

(51) **Int. Cl.**[7] **G06F 13/00**
(52) **U.S. Cl.** **709/222**
(58) **Field of Search** 709/200, 203, 709/220, 218, 221, 222; 713/1, 2, 100

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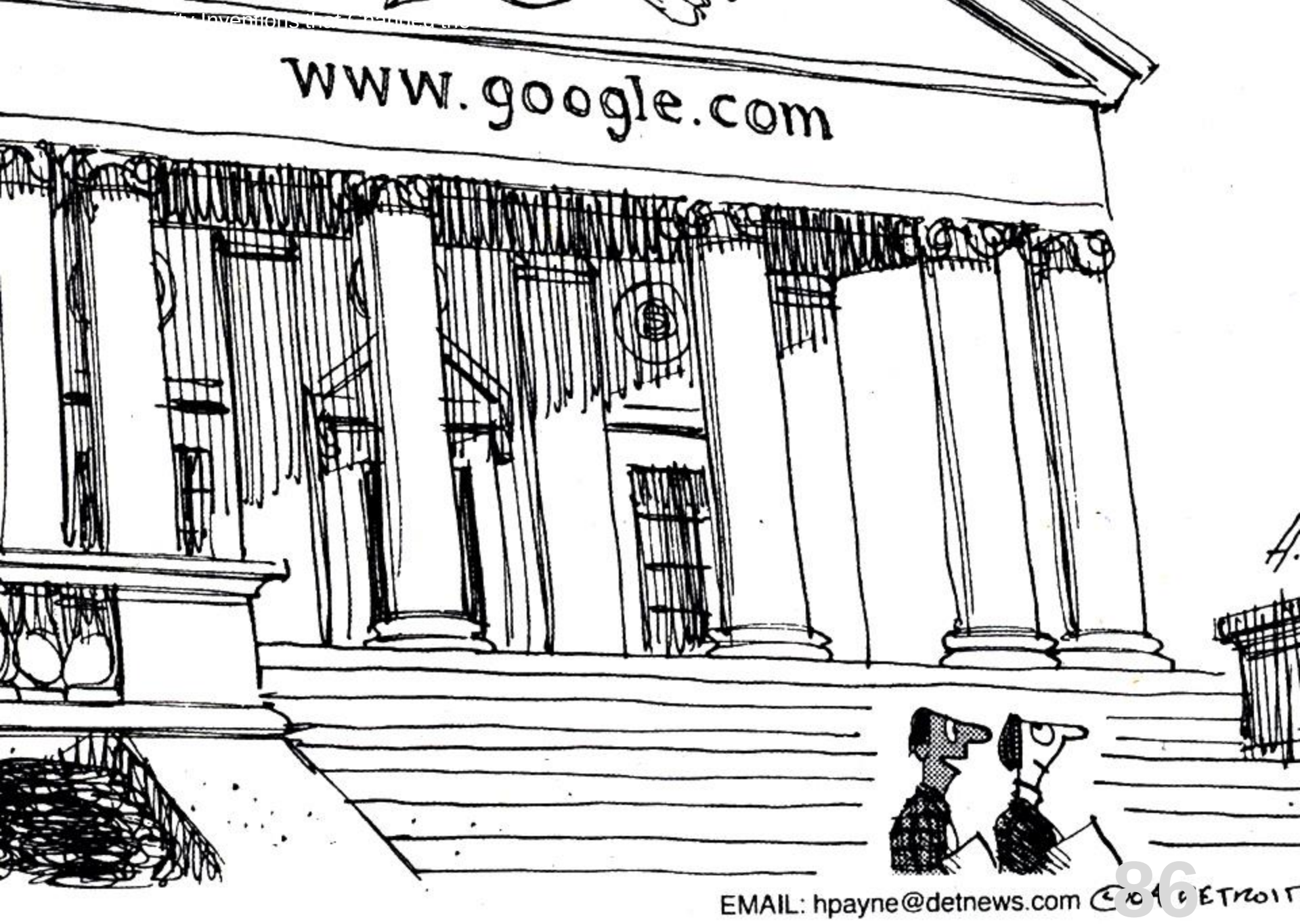
Primary Examiner—Robert B. Harrell
(74) *Attorney, Agent, or Firm*—Chapin & Huang, L.L.C.; Barry W. Chapin

(57) **ABSTRACT**

A network appliance is capable of remote booting and obtaining its configuration information from a source located far away. The network appliance can be shipped to a business location or office environment without requiring a local boot server in that location or environment and without requiring the presence of a person who is familiar with and highly skilled in configuring the appliance. The invention allows for booting and the obtaining of configuration information, and therefore allows for the functioning of the appliance, regardless of whether there is a local server in the local network environment, such as a DHCP server or a boot server, that has been set up and configured to provide to the appliance the booting and configuration information it requires. Self-organizing distributed appliances (SODAs) according to the invention augment the Internet by providing a self-organizing network that efficiently distributes big data items, i.e., data items that cannot be downloaded timely (on demand) over today's networks. One application of self-organizing distributed appliances is the distribution of high-quality video (a half-hour MPEG-1 movies is about one Gbyte). The SODA network alleviates network bottlenecks.

57 Claims, 8 Drawing Sheets

Google



"Formerly known as the school library"

Larry Page **Sergey Brin**

Google

- Both sons of math professors
- Started Ph.D.'s in 1995
- Key patent filed January 1997
  - Funded by NSF – IRI-9411306-4
- Create *Backrub* – precursor to *PageRank*
  - *Rank search results by number and quality of links to a page*
- Stanford marketed technology for 2 years before licensing to Google
  - Turned down an offer from an existing search engine company
  - Stanford felt no commitment to develop
- Stanford finally agreed to license to Brin and Page

US006285999B1

(12) **United States Patent**
Page

(10) **Patent No.: US 6,285,999 B1**
(45) **Date of Patent: Sep. 4, 2001**

9

(54) **METHOD FOR NODE RANKING IN A LINKED DATABASE**

(75) Inventor: **Lawrence Page**, Stanford, CA (US)

(73) Assignee: **The Board of Trustees of the Leland Stanford Junior University**, Stanford, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/004,827**

(22) Filed: **Jan. 9, 1998**

Related U.S. Application Data

(60) Provisional application No. 60/035,205, filed on Jan. 10, 1997.

(51) **Int. Cl.**[7] **G06F 17/30**
(52) **U.S. Cl.** **707/5**; 707/7; 707/501
(58) **Field of Search** 707/100, 5, 7, 707/513, 1–3, 10, 104, 501; 345/440; 382/226, 229, 230, 231

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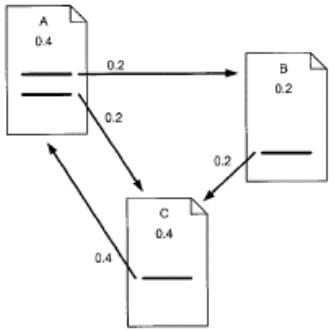
Primary Examiner—Thomas Black
Assistant Examiner—Uyen Le
(74) *Attorney, Agent, or Firm*—Harrity & Snyder L.L.P.

(57) **ABSTRACT**

A method assigns importance ranks to nodes in a linked database, such as any database of documents containing citations, the world wide web or any other hypermedia database. The rank assigned to a document is calculated from the ranks of documents citing it. In addition, the rank of a document is calculated from a constant representing the probability that a browser through the database will randomly jump to the document. The method is particularly useful in enhancing the performance of search engine results for hypermedia databases, such as the world wide web, whose documents have a large variation in quality.

29 Claims, 3 Drawing Sheets



Google

- Company incorporated September 1998 – aged 24 and 25 – in dorm rooms
  - Just like Yahoo
- Name comes from “googol” – 10^{100}
- Initial investment of $100k from Andy Bechtolsheim , Sun Microsystems cofounder
  - Had to incorporate to cash check
- Stanford License signed December 1998, amended May 2000 and October 2003
  - Exclusive patent license through 2011; non-exclusive thereafter
  - Stock -- 1,760,000 shares
  - Annual royalty payment
  - Redacted!

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Google

- Two elements to success:
  - Superior search engine capability
  - Superior business model
    - Selling ads targeting search words *AdWords/AdSense*
    - Auction off rights to specific terms
  - Reshaping media market
- Entire concept was Brin and Page's

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Google

- Brin and Page owned 38,940,000 shares each
- $25 million Series A from Kleiner, Perkins and Sequoia in 1999
- Buried AltaVista, the Digital Equipment search engine
- IPO in August 2004 via unique Dutch Auction method at $85/share
- Quintupled since
- Secondary offering in September 2005 raised
- $8 billion in cash

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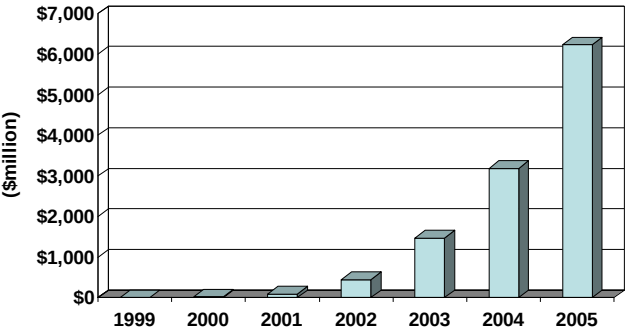
Google Annual Revenues



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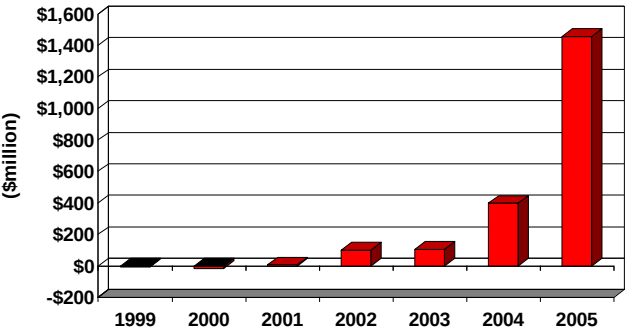
Google Net Income



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Google Stock Price

Wealth Created ($ millions)

Owner	IPO	11/18/05
$/share	$85	$426.80
Brin and Page (Each)	$3,309	$16,620
Stanford	$149	$751
Google Market Cap	$23,240	$116,694

Remember – those are Millions

Stanford actually realized $355 million

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For Comparison

	$ billions
Google	$116
Time Warner	$85
eBay	$65
American Express	$64
Yahoo	$60
Texas Instruments	$53
Sony	$36

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Wealth Created

- **Overall**
  - **5 billionaires**
  - **1,000 millionaires**
  - **Company plane is a 767**
- **Reshaping Silicon Valley**
  - **Leading recruiter**
  - **People starting companies bypassing VC's hoping to sell to Google**

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Conclusion:

Will be the world's most valuable Ph.D. theses

…….if they ever finish!

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Further Reading

- University of Virginia Patent Foundation
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